Final Project Report

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THE STUDY OF PROBABILITY MODEL FOR COMPOUND SIMILARITY SEARCHING

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ABSTRACT

Information Retrieval or IR system main task is to retrieve relevant documents according to the user's query. One of IR most popular retrieval model is the Vector Space Model. This model assumes relevance based on similarity, which is defined as the distance between query and document in the concept space. All currently existing chemical compound database systems have adapt the vector space model to calculate the similarity of a database entry to a query compound. However, it assumes that fragments represented by the bits are independent of one another, which is not necessarily true. Hence, the possibility of applying another IR model is explored, which is the Probabilistic Model, for chemical compound searching. This model estimates the probabilities of a chemical structure to have the same bioactivity as a target compound. It is envisioned that by ranking chemical structures in decreasing order of their probability of relevance to the query structure, the effectiveness of a molecular similarity searching system can be increased. Both fragment dependencies and independencies assumption are taken into consideration in achieving improvement towards compound similarity searching system. After conducting a series of simulated similarity searching, it is concluded that PM approaches really did perform better than the existing similarity searching. It gave better result in all evaluation criteria to confirm this statement. In terms of which probability model performs better, the BD model shown improvement over the BIR model.

ABSTRAK

Tujuan utama sistem pencarian maklumat atau IR (*Information Retrieval*) adalah untuk mencari dokumen yang relevan berdasarkan permintaan pengguna. Salah sebuah model IR yang popular adalah model ruang-vektor. Model in menganggap bahawa sesebuah dokumen itu adalah relevan kepada sesuatu pertanyaan berdasarkan keserupaan antara keduanya. Ia ditakrif sebagai jarak di antara dokumen dan permintaan pengguna (atau *query*), dalam sebuah ruang konsep. Model ruang-vektor ini telah diaplikasikan ke dalam sistem pencarian sebatian kimia yang serupa. Walau bagaimanapun, ia menganggap bit-bit yang mewakili pecahan-pecahan molekul kimia sebagai saling tidak berkait antara satu sama lain. Ini adalah tidak semestinya benar dalam keadaan sebenar. Maka, projek ini mencadangkan perlaksanaan pencarian keserupaan alternatif, iaitu dengan mengaplikasikan sebuah lagi model IR iaitu model kebarangkalian. Model ini akan menganggarkan kebarangkalian samada sesebuah struktur kimia itu mempunyai bioaktiviti yang serupa dengan molekul pertanyaan ataupun tidak. Ini dijangka dapat menghasilkan sebuah sistem yang mempunyai keberkesanan yang lebih baik untuk pengguna. Ini adalah kerana struktur dinilai dan dipaparkan mengikut susunan menurun kebarangkalian sesebuah struktur itu aktif, terhadap pertanyaan pengguna. Kedua-dua anggapan kebersandaran dan ketidaksandaran bit pada struktur kimia, akan dipertimbangkan untuk menghasilkan sistem pencarian keserupaan yang berkesan. Hasil eksperimen menyimpulkan bahawa pencarian keserupaan berdasarkan model kebarangkalian adalah lebih berkesan daripada pencarian keserupaan yang sedia ada. Selain daripada itu, adalah didapati bahawa model kebarangkalian berdasarkan anggapan kebersandaran bit menghasilkan keputusan yang lebih baik berbanding dengan anggapan ketidaksandaran bit.

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CHAPTER 1

INTRODUCTION

1.1 Background of Problem

Cheminformatics is now being extensively used by the pharmaceutical and agrochemical companies, to find new active compounds and bring them to market as quickly as possible. Highly sophisticated systems have been developed for the storage, retrieval and processing of a range of types of chemical information. Although chemical structures differ greatly from other entities that are commonly stored in database, some parallels can be drawn between chemical database searches and searches on words or documents (Miller, 2002). Hence, this project focuses on two different fields: the chemical retrieval system as well as the information retrieval system. Here, an alternative chemical search method is proposed based on the concepts obtained from the information retrieval model.

Information retrieval (IR) is a science or art of locating and obtaining documents based on information needs expressed to a system in a query language. Hence, IR systems need to interpret the content of documents or information items in a collection and rank them according to their degree of relevance. IR systems have

expanded rapidly due to the vast usage of Internet. Many new approaches have been introduced to facilitate user's task in finding information to be used in problem solving and achieving their goals. Previous methods, like the Boolean Model are no longer sufficient in retrieving relevant documents, mainly because it pays little attention to the ranking of the result retrieved and has limited features in query formulation and processing (Croft, 1995). As a result, IR research turns to partial match methods, which consist of two retrieval models: the Vector Space Model (Salton and Buckley, 1988a) and the Probability Model (van Rijsbergen, 1979; Fuhr, 1992). Vector space assumes that relevance is based on similarity measures that are defined as the distance between query and document in the concept space. It represents documents and query by vectors in the space whose elements are their values on the different dimensions. Similarity measure measures the cosines angle between document- vector and query-vector. Probability model on the other hand, estimates the probabilities of relevance or non-relevance of a document to an information need.

Chemical compound databases have now been widely used to assist in the development of new drugs. It has progressed from being a mere repository of compound synthesized within an organisation, to being a powerful research tool for discovering new lead compounds, worthy of further synthetic or biological study. One of the facilities provided for this purpose is the similarity searching tool, in which the database can be searched for compounds similar to a query compound. The main use for this tool is to find other compounds similar to a potential drug compound, with the hope that these similar compounds have similar activity to the query compound and can be better optimised as drugs compared to the initial compound.

Thus, there is always a need to develop new similarity searching methods. This project is an example of an effort to develop a new similarity searching method to help researchers find lead compounds faster and more effectively.

1.2 Problem Statement

Due to the similarities in the way that chemical and textual database records are characterised, many algorithms developed for the processing of textual databases are also applicable to the processing of chemical structure database and vice versa (Willett, 2000). For instance, all existing chemical compound similarity searching systems applies the Vector Space Model (VSM). Even though this approach has acceptable retrieval effectiveness (Salim, 2002), the VSM only considers structural similarity, ignoring both activity and inactivity. Other than that, the evaluation order of the query and the database compounds was not taken into account. It also assumes that fragments are independent of all other fragments, which is not necessarily true (Yates and Neto, 1999).

Hence, this project focuses on developing a similarity searching method based on the Probability Model (PM). It is a stronger theoretical model and there are many approaches in this model (Crestani, *et al.*, 1998). However, only two approaches are used here that are the Binary Independence Retrieval (BIR) Model and Binary Dependence (BD) Model. Their implementation and effectiveness in performing similarity searching has never been experimented or compared with the present similarity searching method.

1.3 Project Objectives

The following are objectives for this project:

a) To develop a new compound similarity searching method which is based on the PM as stated as below:

- BIR model, which is the most simple model and basic of all approaches in PM, assuming linked dependence.
- BD model, which is a more realistic approach in retrieving active structures, where presence or absence of a bit gives effect to the presence or absence of another.

b) To test the effectiveness of each similarity searching method developed based on its ability to give similar active compounds to the target compound.

1.4 Scope

The scope of this project is as follows:

a) Probability-based compound similarity searching is based on the BIR and BD model.

b) Vector space-based compound similarity searching uses the *Tanimoto* coefficient to calculate the similarity measure.

c) All representation of the chemical compound is in the form of binary descriptor. The Barnard Chemical Information (BCI) bit-string is used which is a dictionary-based bit sting.

d) Testing is done on the National Cancer Institute (NCI) AIDS dataset.

1.5 Significance of Study

Many research works have been done on vector space based similarity searching. As mention earlier, it is not without its limitations. Thus, the focus of this

project is to take up other alternatives of IR and apply it in compound similarity searching. PM takes into account both activity and inactivity of a chemical compound, unlike VSM, which only considers structural similarity. Hence, research work should be done to develop a similarity searching based on PM, and compare its effectiveness with the current similarity searching methods.

Currently, there are many similarity searching methods developed and much effort is given in improving them. The question now, is why the need of another similarity searching method? Bajorath (2002) refers to virtual screening of compounds as an "*algorithm jungle*". However, the fact is biological activity is more diverse and complicated than can be addressed by a single method. Different methods rank active compounds differently and thus selecting different subsets of actives. This can lead to the fact that a method can find some actives that all other methods would miss.

Sheridan and Kearsley (2002) mentioned that looking for the best way in searching chemical database can be a pointless exercise. However, the authors also mentioned that multiple methods are still needed, as stated below:

> It is as if we have a set of imperfect windows through which to view Nature. As computational scientists, we get nearer to the truth by looking through as many different windows as possible.
>
> (Sheridan and Kearsley, 2002: 910)

1.6 Organisation of Report

The outline for this research report is as follows:

Chapter 2 covers the literature review of this project, which is divided into 2 parts. The first part discusses about the current similarity searching method. This section will also describe the requirements of similarity searching. Firstly molecular descriptors are discussed. Similarity values obtained depends heavily on the set of descriptors used. Descriptors are vectors of numbers, each of which is based on a predefined attribute. It can be classified into 1D, 2D and 3D. Next, similarity coefficient is discussed. Similarity coefficients are used to obtain a numeric quantification to the degree of similarity between a pair of structures. Basically there are four main types of similarity coefficients that will be discussed, which are distance, association, correlation and probabilistic. The second part explains about the models in IR in terms of the definition and mathematical structures. Both the VSM and PM are discussed. The PM mainly focuses on the BIR and BD model. Discussion is also done in this chapter, to relate both the chemical database and IR domain.

Chapter 3 discuses the methodology used in this project. It covers experimental design as well as performance evaluation. Results of the experiments conducted are recorded in Chapter 4. There is also a discussion which includes critical analysis and result comparison of the performance evaluation done. Finally, Chapter 5 concludes this report.

1.7 Summary

There is always a need to develop new similarity searching methods to find lead compounds more effectively and thus reduce the time needed to develop new drugs. Since, there are resemblances between conducting chemical database searches and searches on documents; hence, this project proposes an alternative chemical search method based on the concepts obtained from the IR domain (i.e. the BIR and BD model). We have discussed in this chapter the objectives, scope and significance of this project, to set the context for the work explained further in the research report.

CHAPTER 2

LITERATURE REVIEW

This chapter is divided into two parts. The first part covers topics on the current chemical database search method emphasizing on how similarity searching complements the early search methods like structure searching and substructure searching. Performance of similarity searching is very much influenced by the similarity coefficient used to measure the likeness between structures. This in turn, depends on how chemical structures are represented. Hence these two requirements are also covered in this chapter.

The second part of this chapter discusses about the models in information retrieval (IR). Both the VSM and PM are discussed. This project focuses on Probability Model. There are many approaches in this model as mentioned by Crestani, *et al.* (1998). However, only two approaches are used here. The first is the Binary Independence Retrieval (BIR) Model, which is a simple model assuming independence of terms. The second approach in probability model is Binary Dependence (BD) Model, which is the opposite of the independence assumptions. It however yields a more realistic approach in retrieving relevant documents.

Discussion is also done in this chapter, to relate both the chemical database and IR domain. Here, the similarity between current compound search method and Vector Space Models is shown. Algorithms developed for the processing of textual databases are also applicable to the processing of chemical structure database (Willett, 2000). This has been the basis of this project. Another alternative in compound similarity searching is proposed that is based on Probability Model. Apart from having a strong theoretical basis, PM is a more realistic approach in retrieval system. It will rank chemical compounds in decreasing order of their probability of being similarly active to the target compound. According to the *Probability Ranking Principle* (PRP), if the ranking of the compounds is in decreasing probability of usefulness to the user, then the overall effectiveness of the system to its users will be the best (Cooper, 1994).

2.1 Searching Methods for Databases of Molecules

There are three different retrieval mechanisms offered by the chemical databases. There are the structure searching, substructure searching and similarity searching. Structure searching and substructure searching are used by the early chemical information systems. There were later complemented by similarity searching, which is the focus of this project.

2.1.1 Structure Searching

Structure searching involves searching for a molecule of database for a specified query molecule. It is also known as the exact-match searching (Miller, 2002). This searching mechanism is done by firstly asking the user to supply the

complete structure of a molecule. At this moment, user must already have a well defined specification on their mind. The database is then searched for compound that matches perfectly with the target structure. Comparison to determine equivalence is done using the graph isomorphism algorithm, where chemical structure is treated as graph. A graph is generated for each compound based on its connection table. Atoms in the chemical structure are denoted as vertices whereas their bonds are denoted by their edges. Searching is done by checking the graph describing the query molecule with the graphs of each of the database molecules for isomorphism. Two graphs are isomorphic if there is 1:1 corresponding between vertices and 1:1 corresponding between edges, with corresponding edges joining corresponding vertices.

Structure searching is performed to find out whether a proposed new structure already exists in a database. This is to ensure that the structure is novel and never been identified before. If it is not in the database, then the new structure is registered in a structure file, also known as a register file, in which there is only a single and unique record of each compound. Some additional information about the new structure can also be recorded in an associated data file. Hence, a structure searching can also be used to get some additional data about a particular compound.

A structure search might yield no hits even though the compound is present in the database. This is depending on the flexibility of the query specification. Other than that, this type of search is also very time consuming. This due to the number of different connection tables that can be constructed for a compound, that is *N!* for *N*-atom molecule (Salim, 2002).

Table 2.1: Overview of structure searching

Structure searching	
Question:	Which molecule in a database matches exactly with the specified structure?
Query requires:	An entire specification of a molecule.
Application:	▪ Identify whether compound exist in database or not. ▪ To get some data about a particular compound e.g. associated biological test results.
Limitation:	▪ Time consuming. ▪ User must already have a well-defined specification to avoid no-hits even though structure is in the database.

2.1.2 Substructure Searching

Substructure searching involves the user specifying a set of pieces of a chemical structure and requests the system to return a set of compounds that contain the pieces. This is done by undergoing detailed atom-by-atom graph matching in which each and every atom and bond in the query substructure is mapped onto the atoms and bonds of each database structure. This is to determine whether subgraph isomorphism is present. However, checking of subgraph isomorphism has an NP-complete nature (Gillet *et al*., 1998), which means that it is totally infeasible to be implemented especially on large databases. This is why, substructure searching has become a two stage procedure, where the first stage involves pre-screening of the database to eliminate structures that cannot possibly match the query. The remaining structure will then undergo the final, time-consuming atom-by-atom search.

Pre-screening of structures can be done by using structural keys. Keys encode the presence or absence of specific structural features. Detailed explanation

is given in the next section. Basically, keys are generated when the structures are registered in the database. A key is created by defining the structural features of interest, assigning a bit (*1* represents presence, *0* represents absence) to each one of these features and generating a bitmap for each compound in the database. At search time, only those structures that have all the keys set by the query structure need to be examined for atom-by-atom mapping.

The purpose of this search mechanism is to find structures containing a specified functional group, thus allowing the properties common to that group to be observed. It can also be used in the implementation of pharmacophoric pattern searching, where compounds containing a specific 3D substructure that has been identified in a molecular modelling study, are sought.

Although substructure searching provides invaluable tool for accessing databases of chemical structures, it does pose several limitations. First, the user posing the query must already have acquired a well defined view of what sorts of structures are expected to be retrieved from the database. They can also tell while browsing the hits, how each answer satisfied the search question. Second, there is very little control on the size of the output produced. For example, the specification of a common ring system can result in retrieval of thousands of compounds from a chemical database. Finally, this search mechanism does not rank the output in order of decreasing probability of activity. It simple divides the database to structures containing the query and those that do not.

Table 2.2: Overview of substructure searching

Substructure searching	
Question:	Which molecules in a database contain the specified structure?
Query requires:	2D or 3D substructure common to actives.
Application:	▪ Find structures containing a specified functional group.
Limitation:	▪ User must already have a well-defined view of what sort of structures are expected to be retrieved. ▪ Little control on the size of output produced. ▪ No ranking mechanism.

2.1.3 Similarity Searching

Limitation of both structure and substructure searching has promoted interest in similarity searching. This search method is based on the similar property principle (Johnson and Maggiora, 1990) where structurally similar molecules will exhibit similar physiochemical and biological properties. Closely related to this principle is the concept of neighbourhood behaviour (Patterson, *et al.*, 1996) which states that compounds within the same neighbourhood or similarity region have the same activity.

Similarity searching is carried out by specifying an entire molecule in the form of a set of structural descriptors. Then, the target molecule is compared with the corresponding set of descriptors for each molecule in the database. Each comparison enables the calculation of a measure of similarity between the target structure and every database structure. Next, the database molecules are then sorted into order of decreasing similarity to the target. The output of the search is a ranked list showing structures judged to be most similar to the target, thus having the

greatest probability of interest to the user. The top structures of the list also show that they are nearest neighbours of the target molecule.

This search mechanism can be use for rational design of new drugs and pesticides. The nearest neighbours for an initial lead compound are sought in order to find better compounds. Other than that, it can also be used for property prediction, where properties of an unknown compound are estimated from those of its nearest neighbour.

Similarity searching has proved to be extremely popular with users. It is especially useful firstly because little information is needed to formulate a reasonable query. No assumption need to be made about which part of the query molecule confers activity. Hence, similarity methods can be used at the beginning of a drug discovery project where there is little information about the target structure and only one or two known actives. Implementations of similarity methods are also computationally inexpensive. Thus, searching large databases can be routinely performed.

There are two factors which influence the definition of molecular similarity, they are: the information used to represent the molecules, and measures used to quantify the degree of structural resemblance between target structure and each of the structures in the database. The following sections further explain these two factors.

Table 2.3: Overview of similarity searching

Similarity searching	
Question:	Which molecules in a database are *similar* to the query molecule?
Query requires:	One or more active molecules.
Application:	• To find better compounds than initial lead compound, for design of new drug or pesticides. • Property prediction of unknown compound.
Why especially useful:	• Little information is needed to formulate a reasonable query. • Computational inexpensive.

2.1.4 Post-searching Processing of Results

After conducting a chemical database search, a user might still face with a list of compounds too large to examined or test. Hence, post search processing of result will be done. It can consist of three approaches, mainly filtering, clustering and human inspection.

Filtering involves imposing secondary search criteria to eliminate compounds. Hence, hit list may be further pruned for compounds having undesirable or non drug like properties. For example compounds might be removed if it cost too much to process or if the molecules have overly reactive groups which could be hazardous. There are also instances where compound resemble each other that there is no point to test all of them. Hence, only representative subset of a larger set is taken in consideration. This is done by clustering similar compounds. Lastly, the last approach involves human inspection which requires great deal of effort and is

very time-consuming. However, it may yield valuable results drawn from insights after seeing a set of structures in the wider context of the research process.

2.2 Representation of Chemical Structures

Selecting compounds requires some quantitative measure of similarity between compounds. These quantitative measures in turn depend on the compound representation or structural descriptors that are amenable to such comparisons. Structural descriptors are actually vectors of numbers, where each of them is based on some-predefined attributes. They are generated from a machine-readable structure representation like a 2D connection table or a set of experimental or calculated 3D coordinates. Molecular descriptors can be classified into 1-dimensional (1D), 2-dimensional (2D) and 3-dimensional (3D) descriptors.

2.2.1 1D Descriptors

1D descriptors model 1D aspect of molecules. It is also known as global molecular properties where physicochemical properties are used as molecular descriptors. Examples of these properties are molecular weight, *ClogP* (log of the octanol / water partition coefficient), molar refractivity (the ratio of the speed of light in a vacuum to its speed in a sample compound) and many more. The main disadvantage of physicochemical properties is that they need to be calculated for every compound in the database and some properties can be extremely time-consuming to calculate.

2.2.2 2D Descriptors

2D descriptors model 2D aspects of molecule obtained from the traditional 2D structure diagram. There are two types of 2D descriptors which are the topological indices and 2D screens. Topological indices characterise the bonding pattern of a molecule by a single value integer or real number. The value obtained is from mathematical algorithms applied to the chemical graph representation of molecules. Thus, each index contains information not about fragments or some locations on the molecule, but rather about the molecule as a whole. The second type of 2D descriptors is the 2D screens, which is the focus of this project and thus explained in detailed in this section.

2D screens refer to bit strings that are used to represent molecules. It was originally developed for substructure search system. 2D screens can be further classified to dictionary-based bit strings and hashed fingerprints. In dictionary-based bit strings, a molecule is split up into fragments of specific functional groups or substructure. Substructural fragments can involve atoms, bonds and rings. Example of fragment types used in 2D screens can be seen in Figure 2.1.

Fragment are recorded in a predefined dictionary of fragments, that specifies the corresponding bit position or screen number of the fragments in the bit string. If a particular fragment is present, then a corresponding bit is set in the bit string. The number of occurrence of the fragment is not recorded in the bit string. Hence if a fragment is present for 100 times, it would only set one bit. It is the number of different types of fragments that determines the number of bits set in a bit string and not its quantity. Examples of dictionary based bit strings are BCI bit strings (Barnard Chemical Information Ltd.) and MDL MACCS key system (Durant, *et al.*, 2002). Figure 2.2 shows the concept of encoding chemical structure as a bit string.

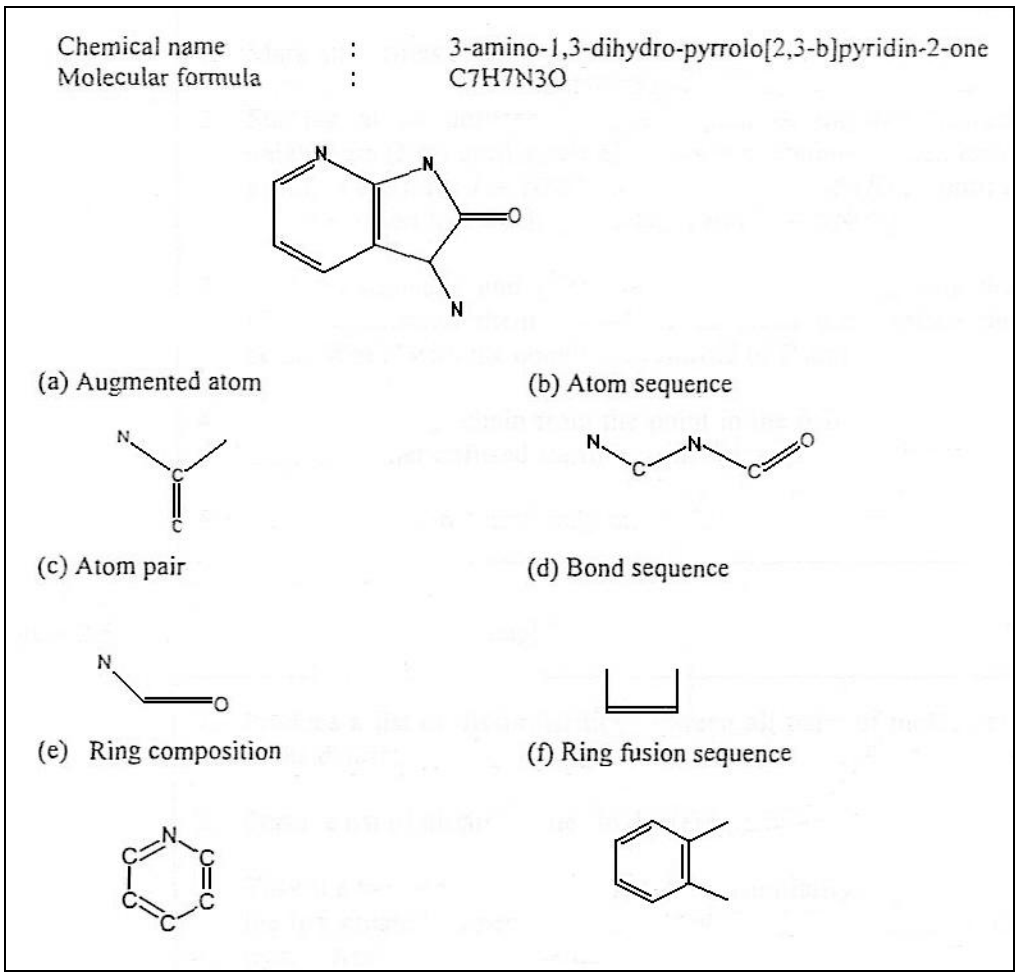


Figure 2.1 Example of fragment types used in 2D screens (Salim, 2002)

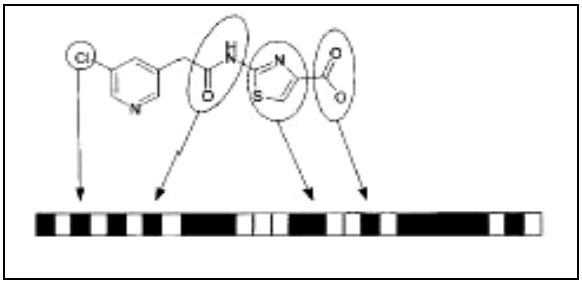


Figure 2.2 Encoding chemical structure as a bit string (Flower, 1997)

Another alternative to dictionary-based bit strings is hashed fingerprint. Unlike the previous bit string, it is not dependent on a predefined list of structural

fragments. Instead, unique fragments that exist in a molecule are hashed using some hashing function to fit into the length of the bit string. Hence, the fingerprints generated are characterized by the nature of the chemical structures in the database rather than by fragments in some predefined list.

Hashed fingerprint adopt the path approach to replace fragment dictionary. By default, all paths through the molecular graph of length 1 to 8 atoms are found. Bits corresponding to each possible type of path are set if present. The resulting bit string is then folded to reduce storage requirements and speed searching. Example of system using hashed fingerprints is the Daylight Chemical Information system (James, *et al.*, 2000). Figure 2.3 shows how bits are set using this approach. A molecule is decomposed into a set of atom paths of all possible lengths. Each of these paths is then mapped to a bit set in a corresponding binary string. Although all existing fragments are included in the hashed fingerprint, it can result in very dense fingerprints. Overlapping of patterns as a result from hashing can also cause loss of information and give false similarity values, as common bits in two strings can be set by completely unrelated fragments.

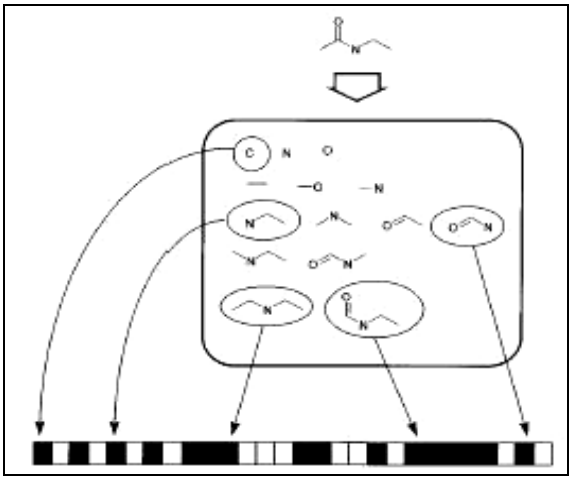


Figure 2.3 Bits set using the path approach (Flower, 1997)

Currently, 2D screens are widely used for database searching, mainly on selecting compounds for inclusion in biological screening programs. This is due to its proven effectiveness (Brown and Martin, 1997), and low processing requirements to calculate similarities between a target structure and large number of structures.

2.2.3 3D Descriptors

3D descriptors model 3D environment of molecules. They have the ability to model the biological activity of molecules because the binding of a molecule to a receptor site is a 3D event. Examples of 3D descriptors are 3D screens, *Potential-Pharmocophore-Point* (PPP) and affinity fingerprints. 3D descriptors however, are computationally more expensive than 2D descriptors. This is because, it does not only involve generating 3D structure but it needs also to handle conformational flexibility and decide which conformers to include. Brown and Martin (1997) also state that 3D fingerprints are not generally superior to 2D representation and that complex designs do not necessarily perform better than simpler ones.

2.3 Similarity Coefficients

One of the most important components of a similarity searching system is the measure that is used to quantify the degree of structural resemblance between the target structure and each of the structures in the database. This measure is called similarity coefficients. This section gives brief overview on types of coefficients used in the chemical database searching, with some common examples. Although there are many ways in expressing similarity coefficient, discussion is limited to the

binary form of the coefficient since this project involves the usage of 2D bit string based similarity measures.

Assume that a chemical structure, S_M is described by listing its set of binary attribute-values or vector, such that $S_M = \{b_{1M}, b_{2M}, b_{3M}, \ \ldots \ b_{nM}\}$, where there are n attributes, and b_{iM} is the value of attribute A_i for structure S_M. The coefficients shown in this section are in binary form, where the presence or absence of bit A_i in the set of bits, is used to represent chemical structures S_M or query S_Q. $Sim_{M, Q}$ is the similarity between molecule M and query molecule Q. There are two ways of expressing the formulae of similarity coefficients, when the data under analysis is in binary form:

a) Formulae based on the 2 x 2 contingency table

   Based on Table 2.4, a is equal to the number of attributes whose value both in S_M and in S_Q is 1, while d is equal to number of attributes whose value both in S_M and in S_Q is 0. b is equal to the number of attributes whose value in S_M is 1 and in S_Q is 0 while c is equal to the number of attributes whose value in S_M is 0 and in S_Q is 1. The sum of all these value ($a + b + c + d$) is equal to the number of attributes, n of each chemical structure. The examples shown in this section uses 2 x 2 contingency table to express the similarity coefficients.

Table 2.4: 2 x 2 contingency table

	$b_{iQ} = 1$	$b_{iQ} = 0$
$b_{iM} = 1$	***a***	***b***
$b_{iM} = 0$	***c***	***d***

b) Formulae based on set theory

   A second alternative is to use the set-theoretic notation, where the following are defined:

- s_m is the set elements b_{iM} in vector $\boldsymbol{S_M}$ whose value is 1,
- s_q is the set elements b_{iQ} in vector $\boldsymbol{S_Q}$ whose value is 1,
- $| s_m |$ refers to the number of elements in set s_m,
- $| s_q |$ refers to the number of elements in set s_q,
- $| s_m \cap s_q |$ refers to the number of elements common to both s_m and s_q,
- $| s_m \cup s_q |$ refers to the number of elements in both s_m and s_q.

$|s_m \cap s_q|$ in this notation is equivalent to a in the previous notation and $|s_m \cup s_q|$ is equivalent to n. $| s_m |$ is equivalent to $a + b$ and $| s_q |$ is equivalent to $a + c$. Hence, we can easily convert from one notation to another. Take for example the *Tanimoto* coefficient below:

	Contingency table	Set theory
Tanimoto	$\frac{a}{a+b+c}$	$= \frac{\lvert s_m \cap s_q \rvert}{\lvert s_m \cap s_q \rvert + \lvert s_m \rvert - \lvert s_m \cap s_q \rvert + \lvert s_q \rvert - \lvert s_m \cap s_q \rvert}$ $= \frac{\lvert s_m \cap s_q \rvert}{\lvert s_m \rvert + \lvert s_q \rvert - \lvert s_m \cap s_q \rvert}$

Figure 2.4 Converting contingency table based formula to set theory based formula.

Even though the first notation is used in this section to express all formulae, however in this project the set theory notation is used in its implementation.

There are four main types of similarity coefficients, which are distance coefficient, association coefficient, correlation coefficients and probabilistic coefficients. The origins of these coefficients can be found in the review paper by Ellis, *et al.* (1994). They are all briefly explained below:

a) Distance coefficient

This coefficient is used to measure the distance between structures in a molecular space. It is difficult to visualise the geometry of a space of more than 3 dimensions (hyperspace). Hence to preserve the validity of geometric distances between objects in a hyperspace, the coefficient must have the property of metrics. In order to do so, a distance coefficient needs to obey certain rules:

- Distances must be zero or positive: $Sim_{M, Q} \geq 0$
- Distances from object to itself must be zero: $Sim_{M, Q} = Sim_{Q, M} = 0$
- Distance between non-identical objects must be greater than zero: If $S_M \neq S_Q$, then $Sim_{M, Q} > 0$
- Distance must be symmetric: $Sim_{M, Q} = Sim_{Q, M}$
- Distance must obey the triangular inequality: $Sim_{M, Q} \leq Sim_{M, X} + Sim_{Q, X}$

Table 2.5: Examples of distance coefficients (Ellis, *et al.*, 1994)

Coefficient	Binary Formula
Mean Manhattan	$\frac{b+c}{n}$
Mean Euclidean	$\frac{\sqrt{b+c}}{n}$
Mean Canberra	$\frac{b+c}{n}$
Divergence	$\frac{\sqrt{b+c}}{\sqrt{n}}$

b) Association coefficient

Association coefficient is a pair-function that can measure the agreement between the binary, multi-state or continuous character representations of two molecules. It is based on the inner product of corresponding elements of two vectors denoted by *a*. The basic formula of an

association coefficient for binary data is formed by dividing *a*. The following table shows examples of association coefficients:

Table 2.6: Examples of association coefficients (Ellis, *et al.*, 1994)

Coefficient	Binary Formula
Jaccard / Tanimoto	$\frac{a}{a+b+c}$
Ochiai / Cosine	$\frac{a}{\sqrt{(a+b)(a+c)}}$
Dice	$\frac{2a}{2a+b+c}$
Russell / Rao	$\frac{a}{n}$
Sokal / Sneath	$\frac{a}{a+2b+2c}$

c) Correlation coefficient

This coefficient measures the degree of correlation between sets of values representing the molecules, like the proportionality and independence between pairs of real-valued molecular descriptors. The following table shows examples of correlation coefficients:

Table 2.7: Examples of correlation coefficients (Ellis, *et al.*, 1994)

Coefficient	Binary Formula
Pearson	$\frac{ad-bc}{\sqrt{(a+b)(a+c)(b+d)(c+d)}}$
Yule	$\frac{ad-bc}{ad+bc}$
McConnaughey	$\frac{a^2-bc}{(a+b)(a+c)}$

Stiles	$\log_{10} \frac{n\left(\lvert ad-bc\rvert - \frac{n}{2}\right)^2}{(a+b)(a+c)(b+d)(c+d)}$
Dennis	$\frac{ad-bc}{\sqrt{n(a+b)(a+c)}}$

d) Probabilistic coefficient

Probabilistic coefficient focuses on distribution of the frequencies of descriptors over the members of a data set, giving more importance to a match on an infrequently occurring variable. However, this type of coefficient is not much used in measuring molecular similarity due to its poor performance and extremely extensive computations requirement (Adamson and Bush, 1975).

2.4 Information Retrieval (IR)

Information retrieval is a science or art of locating and obtaining documents based on information needs expressed to a system in a query language (Losee, 1997). Normally, people mistakenly refer to it as data retrieval. Instead, data retrieval involves retrieving data from tables that have rows and columns. It is then organized and presented in a manner that provides information to users. However, in documents, there are no tables or columns to refer to, making it difficult in terms of seeking and retrieving such information. Hence it can be concluded that data retrieval system deals with data that has a well-defined structure and semantic, for example the database system. It is not suitable for use in retrieving information about a subject or topic.

IR system needs to interpret the content of the documents or information items in a collection and rank them according to their degree of relevance. It focuses on two main issues:

a) Extracting the semantic information from the document text,

b) Match it with user's request and determine their degree of relevance.

Recently, IR has taken the centre stage. Before the World Wide Web (WWW) is introduced, finding and retrieving information has depended on an intermediary such as librarians or other information experts. This field used to be considered as too esoteric for a typical user. The Web is an enormous repository of knowledge and culture. Now, every group of users can use it to find information. Its success is due to its standard user interface that hides the computational environment running it. Since the Web is vast and unknown, how does one find information? Surely by navigating through the Web would be a tedious and inefficient way of doing it.

Matters are made worst when there is no well-defined underlying data model for the Web. Hence, IR research is now an important component in major information services and the Web. Its goal is to facilitate convenient retrieval of information regardless of its form, medium or location.

2.4.1 Retrieval Process

To show how retrieval is done, consider the following example. Below is a user information need:

Find all documents containing information on the crime rate in Kuala Lumpur involving teenagers.

In order to be relevant, the result must include statistic of crime rates in Kuala Lumpur that only involves teenagers. The user must then translate this information into a query, which can be processed by the IR system. Translation usually produces

set of keywords or index terms, which represent the description of the user's information need.

IR system then retrieve document which might be useful or relevant to the user, ranking it according to a likelihood of relevance, before showing it to the user. Normally, the results will not be good, as most users do not know how to formulate their query out of their information needs.

The user then examines the set of ranked documents for useful information. At this point, user can pinpoint a subset of useful document and initiate a user feedback cycle, which is based on the documents selected by the user. The system then changes the query formulation. This modified query is a better representation of the user's need and hence, a better retrieval.

2.4.2 Classical Retrieval Model

In IR models, the following elements are given:

a) A finite set of identifier (e.g. keyword, terms)

b) A finite set of documents where a document can be a collection of some other objects or modelled as a series of weights. Weights refers to the degree to which identifier relate to a particular document.

c) A finite set of criteria (e.g. relevance, non-relevance), according to which two documents are compared to each other. The result of this comparison is a score assigned to that pair of documents.

Classical retrieval is a process of associating documents to a query, which the scores are greatest, based on a given criterion (Dominich, 2000). As described earlier, IR involves documents, denoted by d and a given query, q. Retrieval involves the task of finding these documents, which implies the query ($d \rightarrow q$).

Initially, *Boolean* retrieval model was used to do this task. A review of this model as well as other classical retrieval models can be found in Fuhr (2001). *Boolean* model is part of the exact matching methods category, where the query are normally represented by *Boolean* statements, consisting of search terms interrelated by the *Boolean* operators *AND*, *OR* and *NOT*. The retrieval system will then select those stored items that are identified by the exact combination of search terms specified by the query. Given a four-term query statement such as "(*A* ***AND*** *B*) **OR** (*C* ***AND*** *D*)", the retrieved items will contain either the term pair *A* and *B* or the pair *C* and *D* or both pairs.

Retrieval performance of the *Boolean* model depends on the type of search request submitted and on the homogeneity of the collection being searched (Blair and Maron, 1985). Specific queries may lead to only a few items being retrieved but are most likely to be useful. On the other hand, when query are broadly formulated, many more stored items are retrieved, including both relevant and irrelevant items. Retrieval performance is also generally better when the stored collection covers a well-defined subject, compared to those covering many different topic areas.

This model has been widely accepted, because *Boolean* formulations can be used to express term relationships such as synonym relations identified by the *OR* operators and term phrases specified by the *AND* operators. Furthermore, fast responses are obtained even for very large document collections.

Unfortunately, *Boolean* model posses some disadvantages. Firstly, all retrieved documents are assumed to be equally useful. This approach also has no ranking system. Thus it acts more like a data retrieval model rather than an IR model. Secondly, successful retrieval mainly requires a very well formed query and good search keys. This is not likely since that the users have problem specifying their information needs. The document representations itself are imprecise, since IR system has only limited processing methods that can represent the semantics of a document. Certainly, this would lead to retrieval of too few or too many documents.

Thus, IR research turns to partial match methods category to overcome the limitation of the *Boolean* approach. It consists of two retrieval models that is Vector Space Model (VSM) and Probability Model (PM). VSM is based on index term weighting. These term weights are used to compute the degree of similarity between each documents stored in the system and the user query. Then, the retrieved documents are sorted in decreasing order of this degree of similarity. PM on the other hand, captures the IR problem within a probabilistic framework. The model tries to estimate the probability that the user will find the document interesting or relevant. It then presents to the user ranked documents in decreasing order of their probability of relevance to the query. In contrast to the *Boolean* model, both of these approaches take into consideration documents, which match the query term only partially. As a result, the ranked documents retrieved, are more precise than the documents retrieved by the *Boolean* model (Yates and Nato, 1999). The following sections explain these models in more detail.

2.5 Vector Space Model (VSM)

The VSM (Salton and Buckley, 1988a), represents both the documents and queries as a vector of terms. Given a document D_j and a query q characterised by a

vector, such that $D_j = \{t_{1j}, t_{2j}, t_{3j}, ..., t_{nj}\}$ and $q = \{t_{1q}, t_{2q}, t_{3q}, ..., t_{nq}\}$, where there are n elements. Elements t_{ij} or t_{iq} is a value representing either:

a) The presence or absence of term t_i in the set of terms that is used to represent document D_j or query q in which the data are in binary form. Here, every term is treated equally. One may argue that this does not reflect real life situation, where one term may have more importance than others. Hence, the second approach is being employed as explained below.

b) The weight of term t_i in the set of terms that is used to represent documents D_j or query q, in which data are in non-binary form. Here, term weights are used to distinguish the degree of importance of the terms.

Various schemes exist for term weighting (Salton and Buckley, 1988b; Sparck Jones, 1973; Yu *et al.*, 1982). The formula that each uses to calculate weights are made up of some combination of functions based on the factor *term frequency* (tf_{ij}), which is the raw frequency of a term t_i inside document D_j. Consider a collection C of objects and a user's query which is a vague specification of a set A of objects. *tf* factor refers to as local weight, where it is used to determined the intra-cluster similarity. Intra-cluster similarity is where one needs to determine what features better describe the objects in the set A. Sparck Jones (1973) added an *inverse document frequency* (*idf*) factor. This factor is a global weight which measures the inter-clustering dissimilarity, where one needs to determine what features better distinguish the objects in set A from the remaining objects in C. Thus, the inverse document frequency form term t_i is defined as:

$$idf_i = \log (N / df)$$

where N refers to number of document in collection and df is the number of document that contains t_i. Hence, the document indexing weight (w_{ij}) of term t_i with respect to document D_j, is given by:

$$w_{ij} = tf_{ij} \text{ x } idf_i$$

In this model, both document and query representations are described as points in T dimensional space, where T is the number of unique terms in the document collection. Figure 2.5 shows an example of a VSM representation for a system with three terms.

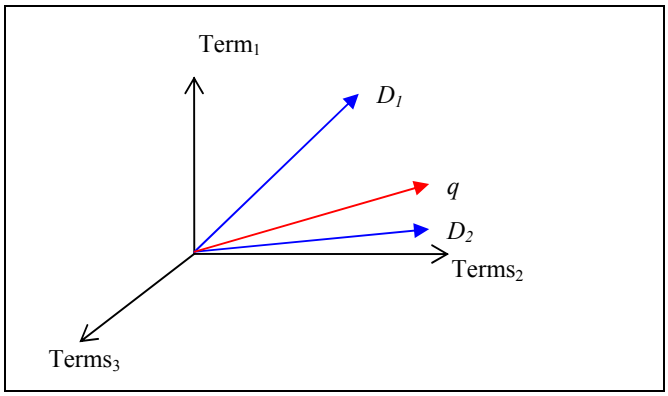


Figure 2.5 Three dimensional vector space.

Each axis in the space corresponds to a different term. The position of each document vector in the space is determined by the weight of the terms in that vector, which is discussed previously. Here, there is just one criterion considered, which is relevance. Similarity between query and document is measured by a function that determines the matching terms in the respective vectors in order to identify the relevant documents. This function is also referred to as the similarity measure which has three basic properties:

a) It has a value between 0 to 1,

b) It does not depend on the order of which the document are being compared, and

c) If the value is equal to 1, then the query vector is the same as the document vector.

A common example of similarity measure is the *Cosine* coefficient, which evaluate the degree of similarity of document with regards to the query q, as the distance between the vector D_j and q. This distance can be quantified by using the cosine angle between there two vectors, which is given below:

$$Sim(D_j, q) = \frac{\sum_{i=1}^{t} w_{ij} \times w_{iq}}{\sqrt{\sum_{i=1}^{t} (w_{ij})^2 \times \sum_{j=1}^{t} (w_{iq})^2}}$$

Based on this explanation, we can determine that in Figure 2.5, the documents D_2 is more similar to the query q, due to its distance being nearer to q compared to D_1. Other than the Cosine coefficient, there are also other similarity measures used in text retrieval as listed by Ellis, *et al*. (1994).

Values obtained from the similarity measures are next used to produce ranked list of relevant document. They are sorted in decreasing order of the measures. Documents are said to be retrieved if their similarity measures exceeding a threshold value which is normally requested from the user.

The VSM is a popular retrieval model especially among the Web community. It is either superior or almost as good as other alternative (Yates and Nato, 1999). This is due to its approach that is known for being simple and very effective in retrieving information. The following is the rest of the main advantages of this model:

a) Documents are ranked according to their degree of similarity to the query.

b) Partial matching strategy allows retrieval of documents that approximate the query condition.

c) Term weighting scheme improves retrieval performance.

However, the model is not without its drawbacks. The disadvantages of this model are stated below:

a) In VSM, terms are assumed to be mutually independent, for example the following figure. Assume that a complete concept space, U is form by a set of terms: $U = t_1 \cup t_2 \cup t_3 \cup t_4$. The term t corresponds to the disjoint basic concepts: $t_i \cap t_j = \emptyset$ for $i \neq j$. As a result, terms form a dissection of U. However, in practice, terms are not necessarily independent of all other terms.

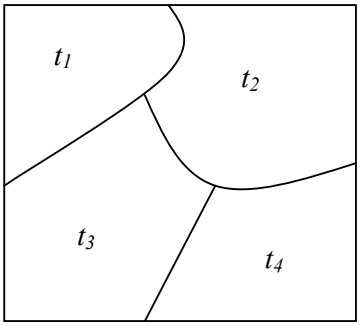


Figure 2.6 Disjoint concept of U

b) Even though this model is simple, its ranked answer sets are difficult to improve on without query expansion or relevance feedback within the framework of the vector model (Yates and Neto, 1999).

2.6 Probability Model (PM)

In the PM, formal probability theory and statistics are used to estimates the probability of relevance by which the document are ranked. This methodology is to

be distinguished from looser approaches like the VSM, in which the retrieved items are ranked by a similarity measures whose values are not directly interpretable as probabilities.

Given a document (*D*), a query (*q*) and a cut-off numeric value of probability., this model computes the conditional probability *P(D|R)* that a given document *D* is observed on a random basis given relevant event *R*, that the document is relevant to the query (van Rijsbergen, 1979). Query and document are represented by a set of terms. Then *P(D|R)* is calculated as a function of the probability of occurrence of these terms in relevant against non-relevant documents. The term probabilities are similar to the term weights in the VSM. However, a probabilistic formula is used to calculate *P(D|R)*, in place of the similarity coefficient used to calculate relevance ranking in VSM. The probabilistic formula depends on the specific model used, and also on the assumptions made about the distribution of terms. An overview of the many probabilistic models developed can be seen in Crestani, *et al.* (1998). This project however focuses on only two models as explained in later sections (BIR and BD models).

Next, documents with relevance probability exceeding its non-relevance probability are ranked in decreasing order of their relevance. Documents are said to be retrieved when their relevance probability exceed the cut-off value. According to the *Probability Ranking Principle* (PRP), retrieval system effectiveness is optimal if documents are ranked according to their probability of relevance. The justification of this system principle is as follows: Let *C* denotes the cost of retrieving a relevant document and $\overline{C}$ as costs for retrieving a non-relevance document. A user prefers relevant documents, and thus $\overline{C} > C$ is assumed. Then the *expected cost* (*EC*) for retrieving a document *D* is computed as:

$$EC(D) = C \cdot P(R \mid D) + \overline{C} \cdot (1 - P(R \mid D))$$

where *P(R|D)* refers to the probability of relevant documents and 1- *P(R|D)* = *P(NR|D)* refers to probability of non-relevant documents.

In a ranked list of documents, a user will look at the document and stops at an arbitrary point. In order to minimize the sum of expected cost at any cut-off point, documents have to be ranked in the order of the increase of expected cost. For example, for any two documents D_1 and D_2, rank D_1 ahead of D_2 if $EC(D_1) < EC(D_2)$. Due to $\overline{C} > C$, this condition is equivalent to $P\ (R \mid D) > P\ (NR \mid D)$. Hence, documents are ranked to decreasing probability of relevance, in order to minimize the expected cost. So, here it can be seen that probabilistic retrieval models are directly related to retrieval quality.

The evaluation order, whether document to query or vice versa, also matters in this model. The conditional probability $P(q|D)$ measures the exhaustivity of a document that responds to a query. Whereas, conditional probability $P(D|q)$ can be used as a measure of specifity. Figure 2.7 shows the differences of both evaluation orders with t_i corresponding to term i. In another example, consider the encyclopaedia as our document. The encyclopaedia contains a large number of terms, which mean that it can answer many queries. Thus, a high value of $P(q|D)$. However, only a small part of this document will be relevant in most cases. This is measured by $P(D|q)$.

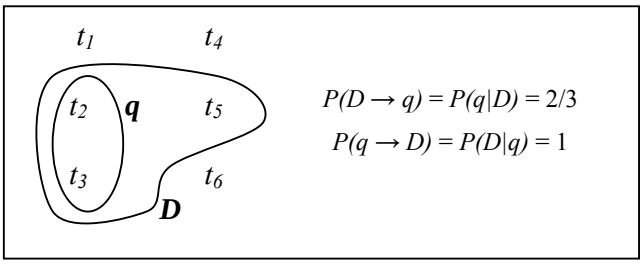


Figure 2.7 $P(q|D)$ vs. $P(D|q)$ (Fuhr, 2001)

Based on these advantages of PM, we can conclude that PM has strong theoretical basis and in principle should give the best predictions of relevance given available information. Yet, probabilistic methods have not yet been widely used. This is because some researchers feel that the formulation of exact statistical

assumptions is an unnecessary theoretical burden. They would rather spend the time and effort on looser formalisms and simpler approach than the probability theory. There is also the need to guess the initial separation of documents into relevant and non-relevant sets, and ongoing training collection with relevance information in order to provide clues about the documents when computing the conditional probability *P(D|R)*.

2.6.1 Binary Independence Retrieval (BIR) Model

The BIR model (van Rijsbergen, 1979; Fuhr, 1992) is the simplest of all probabilistic models. It is based on the presence or absence of independently distributed terms in relevant and non-relevant documents. This means that the probability of any given term occurring in a relevant document is independent of the probability of any other term occurring in a relevant document and similarly for non-relevant documents. Hence, the name *Binary Independence*.

This model takes into account the non-disjoint concepts, where with term t_i and t_j, $t_i \cap t_j \neq \emptyset$. Hence, terms are map onto disjoint atomic concept by forming conjuncts of all term t, in which each term either occurs positively or negated. Hence, a document, D is represented as:

$$D = t_1^{\alpha_1} \cap \ldots \cap t_n^{\alpha_n} \quad \text{with} \quad t_i^{\alpha_i} = \begin{cases} t_i \text{ if } \alpha_i = 1 \\ \overline{t_i} \text{ if } \alpha_i = 0 \end{cases}$$

t_i refers to the term t at location i on the document vector. Whereas, α_i acts as a binary selector that is, if $\alpha_i = 1$, then it means that the term occurs in the document, otherwise it is 0 and assumed negated. For example, consider the following diagram, which illustrates a disjoint concept of three terms namely t_1, t_2 and t_3, with D_i, referring to documents. The complete conjuncts of terms are as follows:

$$D_0 = \overline{t_1} \cap \overline{t_2} \cap \overline{t_3} \qquad D_1 = t_1 \cap \overline{t_2} \cap \overline{t_3}$$
$$D_2 = \overline{t_1} \cap t_2 \cap \overline{t_3} \qquad D_3 = \overline{t_1} \cap \overline{t_2} \cap t_3$$
$$D_4 = t_1 \cap t_2 \cap \overline{t_3} \qquad D_5 = t_1 \cap \overline{t_2} \cap t_3$$
$$D_6 = \overline{t_1} \cap t_2 \cap t_3 \qquad D_7 = t_1 \cap t_2 \cap t_3$$

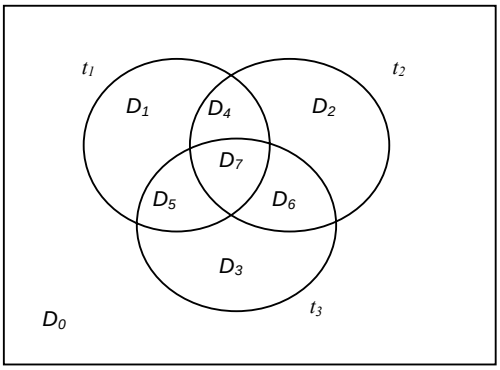


Figure 2.8 Construction of disjoint concepts for the case of 3 terms

2.6.1.1 Retrieval Status Value (RSV)

Retrieval status value refers to the similarity function that estimates ranking score of a particular document against the query posted by the user. The optimal ranking function is given as *P(R|D)* / *P(NR|D)*. *P(R|D)* refers to the conditional probability of relevant documents whereas *P(NR|D)* refers to the conditional probability of non-relevant documents. In order to estimate the probability of relevant and non-relevant documents, we consider the *Bayes* theorem where:

$$P(R \mid D) = \frac{P(R) \cdot P(D \mid R)}{P(D)}$$

$$P(NR \mid D) = \frac{P(NR) \cdot P(D \mid NR)}{P(D)} \qquad (2.1)$$

where $P(D|R)$ is the probability of a relevant document,
$P(D|NR)$ is the probability of a non-relevant document,
$P(R)$ is the probability of relevance,
$P(NR)$ is the probability of non-relevance,
$P(D)$ is the probability of the document.

Thus, by substituting the optimal ranking function with the expression in (2.1), we get:

$$\frac{P(R \mid D)}{P(NR \mid D)} = \frac{P(R) \cdot P(D \mid R)}{P(NR) \cdot P(D \mid NR)} \qquad (2.2)$$

Efficient matching requires data on the terms presence or absence in documents. Other than that, it also requires terms presence probabilities in relevant and non-relevant documents. Hence, two variables were defined, which are:

a) p_i that refers to the probability that a term appearing in a relevant document (R). The complement of p_i, denotes the probability of absence of a term in R.

b) q_i that refers to the probability that a term appearing in a non-relevant document (NR). The complement of q_i, denotes the probability of absence of a term in NR.

Let α_i refers to as a binary selector, as mentioned before. Now, the probability of relevance of a document $P(D|R)$ is given as:

$$P(D \mid R) = \prod_{i=1..n} (p_i)^{\alpha_i} (1 - p_i)^{1-\alpha_i}$$

where $p_i = P(\alpha_i = 1 \mid R)$ and $(1-p_i) = P(\alpha_i = 0 \mid R)$. Whereas, the probability of non-relevance of a document $P(D \mid NR)$ is given as:

$$P(D \mid NR) = \prod_{i=1..n} (q_i)^{\alpha_i} (1 - q_i)^{1-\alpha_i}$$

where $q_i = P(\alpha_i = 1 \mid NR)$ and $(1-q_i) = P(\alpha_i = 0 \mid NR)$.

Thus, by substituting both the above expression in (2.2), the ranking function becomes:

$$\frac{P(R \mid D)}{P(NR \mid D)} = \prod_{i=1..n} \left(\frac{p_i(1-q_i)}{q_i(1-p_i)} \right)^{\alpha_i} \cdot \left(\frac{1-p_i}{1-q_i} \right) \cdot \frac{P(R)}{P(NR)} \tag{2.3}$$

Then, by taking the logs of the ranking function, it will transform (2.3) into a linear discriminate function:

$$\begin{aligned} \frac{P(R \mid D)}{P(NR \mid D)} &= \sum_{i=1}^{n} \alpha_i \log \left(\frac{p_i(1-q_i)}{q_i(1-p_i)} \right) + \log \left(\frac{1-p_i}{1-q_i} \right) + \log \frac{P(R)}{P(NR)} \\ &= \sum_{i=1}^{n} c_i \alpha i + C \\ &= \sum_{b_i \in D \cap q} c_i \alpha i \end{aligned} \tag{2.4}$$

The constant C, which has been assumed the same for all documents, will vary from query to query. It can be interpreted as the cut-off value applied to the retrieval function. c_i indicates the capability of a term to discriminate relevant from the non-relevant document. It is also referred to as relevance weights or term relevance.

2.6.1.2 Probability estimation and improvement

There are two instances in probability estimation. If we already know the set of relevant documents R, c_i can be interpreted with assistance of the following table. Let N be the number of documents in the database and R refers to the number of relevant documents. n refers to the number of documents which contain term t_i, whereas r refers to the number of relevant documents which contain term t_i.

Table 2.8: Contingency table for estimating c_i (van Rijsbergen, 1979)

	Relevant	Non-relevant	
$\alpha_i = 1$	r	n-r	n
$\alpha_i = 0$	R-r	N-n-R+r	N-n
	R	N-R	N

p_i can be estimated as r/R whereas q_i can be estimates as $(n\text{-}r) / (N\text{-}R)$. Hence, the c_i can be rewritten as:

$$c_i = \log \frac{r(N - R - n + r)}{(n - r)(R - r)}$$

The last formula for p_i and q_i can create problems for small values of R and r_i which normally is the case in real situation (Yates and Neto, 1999). To avoid these problems, an adjustment factor is often added in which yield:

a) $p_i = (r_i + 0.5) / (R + 1)$

b) $q_i = (n_i - r_i + 0.5) / (N - R + 1)$

The second instance in estimating probability of p_i and q_i is when we do not know the set of relevant documents R at the beginning. Hence, it is necessary to devise a method for initially computing the probabilities $P(D|R)$ and $P(D|NR)$. In the beginning, they are no retrieved documents. Thus, the following assumption is made:

a) p_i is assumed a constant for all index term t_i. Usually, the value 0.5 is selected:

$$p_i = 0.5$$

b) q_i or the distribution of index terms among the non-relevant documents can be approximated by the distribution of index terms t_i (n_i) among all the document in the collection (N):

$$q_i = n_i / N$$

As a result, documents which contain query terms are retrieved and provided an initial probabilistic ranking for them. This is then improved by the following probability estimation improvement process. Let V be a subset of documents initially retrieved and ranked by the BIR model. Such a subset can be defined, for instance, as the top r ranked documents where r is a defined threshold. Additionally, let V_i be the subset of V containing term t_i. Hence, the following assumption is made:

a) p_i can be approximated by the distribution of the index term t_i among the documents retrieved so far:

$$p_i = V_i / V$$

b) q_i can be approximated by considering all the non-retrieved document that are non-relevant:

$$q_i = (n_i - V_i) / (N - V)$$

This process can then be repeated recursively and it is now possible to improve the estimation on *P(D|R)* and *P(D|NR)* without any assistance from a human subject. However, we can also ask assistance from the user for definition of the subset V. The same adjustment factor is also added in calculating p_i and q_i to overcome problems due to small values of V and V_i.

c) $p_i = (V_i + 0.5) / (V + 1)$

d) $q_i = (n_i - V_i + 0.5) / (N - V + 1)$

2.6.2 Binary Dependence (BD) Model

Most IR models assume terms of query and documents are independent from each another. This assumption of terms independence is a matter of mathematical convenience and hence yields to simplistic retrieval system. Research work by Bollmann-Sdorra and Raghavan (1998) showed that, for retrieval functions such as the cosine used in the VSM, weighted retrieval is incompatible with term independence in query space. They also proved that the term independence in the query space even turned out to be undesirable.

The hazard of term independence is also pointed out by Cooper (1995), mainly on data inconsistency. He also stated that the BIR model, discussed in the previous section, is mistakenly named and better referred to as linked-dependence model. This model has been called *Binary Independence*, because simplified assumption is made, where document properties that serve as clues to relevance are independent of each other in both set of relevant documents and the set of non-relevant documents. However, Cooper stated that BIR model does exhibit weaker link-dependence. Although this is very much debatable, it has at least the virtue of not denying the existence of dependencies. Link-dependence is based on one important assumption:

$$\frac{P(A,B \mid R)}{P(A,B \mid NR)} = \frac{P(A \mid R)P(B \mid R)}{P(A \mid NR)P(B \mid NR)}$$

where A, B are regarded as properties of documents and R designates the relevance set whereas NR designates the non-relevance set. The degree of statistical dependence of documents in the relevant set is associated in a certain way with their degree of statistical dependence in the non-relevant set.

Hence, the correct procedure is to assume dependence of terms and thus creating a more realistic retrieval system. Term dependencies exist when the relationships between terms in document are such that the presence or absence of one term provides information about the probability of the presence or absence of another

term (Loose, 1994). Based on this assumption, many probabilistic models were proposed to remove the independence assumption. For example, the Bahadur Lazarsfeld Expansion or BLE (Losee, 1994) and tree dependence model (van Rijsbergen, 1979). The tree dependence model exhibits a number of advantages over the exact model provided by the BLE expression. It is also more easily computed than the BLE expansion (Salton, *et al.*, 1983). Tree dependence model applies the approach suggested by Chow and Liu (1968) to capture term dependence, where an MST is constructed using mutual information, for a dependence tree. Also from this approach is the *Chow Expansion*, which was originally used in the pattern recognition field. However, it has been applied in probabilistic IR as done by Lee and Lee (2002) and hence will be the focus of this project.

Instead of just considering the absence or presence of individual terms independently, one selects certain pairs of terms and calculates a weight for them jointly. Assume vector $D = \{t_1, t_2 \ldots t_n\}$ are binary values. Dependence can be arbitrarily complex as follows:

$$P(D) = P(t_1 \ldots t_n) = P(t_1)P(t_2 \mid t_1)P(t_3 \mid t_1, t_2)\ldots P(t_n \mid t_1, t_2 \ldots t_{n-1}) \qquad (2.5)$$

in which we need to condition each variables in turn by steadily increasing set of other variables, to capture all dependence data. This is computationally inefficient and impossible if we do not have sufficient data to calculate the high order dependencies. Hence, another approach is taken to estimate *P(D)*, which captures the significant dependence information. $P(t_i \mid t_{i-1} \ldots t_1)$ is solely dependent on some preceding variable $t_{j(i)}$. In other words, we obtained:

$$P(D) = \prod_{i=1}^{n} P(t_i \mid t_{j(i)}) \qquad 0 \le j(i) \le i \qquad (2.6)$$

A probability distribution that can be represented as in the above expression is called a probability distribution of first-order tree dependence (Chow and Liu, 1968). For example the Figure 2.9, according to equation (2.6), the probability of a structure can be written as $P(t_1)\ P(t_2|t_1)\ P(t_3|t_2)\ P(t_4|t_2)\ P(t_5|t_2)$, or the following product expansion:

$$P(t_1)P(t_2|t_{j(2)})\ P(t_3|t_{j(3)})\ldots\ P(t_n|t_{j(n)})$$

where the function *j(i)* exhibits the limited dependence of one bit on preceding bits.

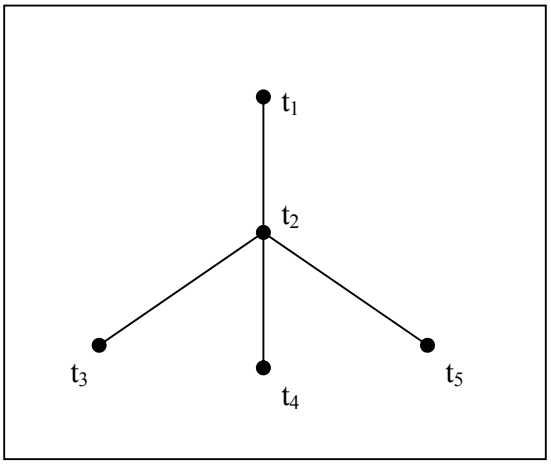


Figure 2.9 Term dependence tree

2.6.2.1 Dependence Tree

A dependence tree is an obvious method for identifying the most important pairwise dependencies and the best mapping of *j(i)*. Chow and Liu (1968) suggest constructing a *Maximum Spanning Tree* or MST (Whitney, 1972). The nodes are used to represent the individual terms and the branches between pairs of nodes, which designates the pair wise similarities or dependencies. To construct an MST for a set of entities, we need to identify the most important similarities between pairs of entities. *Expected Mutual Information Measure* or EMIM is a criterion for measuring this similarity or dependence between pairs (Crestani *et al.*, 1995). Hence, an MST is a tree that includes every node and maximizes the sum of EMIM. EMIM is defined as follows:

$$I(t_i,t_j) = \sum_{t_i,t_j} P(t_i,t_j)\log\frac{P(t_i,t_j)}{P(t_i)p(t_j)}$$

where the sum is taken over all combinations of values of term t_i and t_j (either 0 or 1) and $P(t_i, t_j)$, $P(t_i)$ and $P(t_j)$ are computed as the proportion of documents in the collection containing respectively both terms t_i and t_j.

Table 2.9: Simple maximum likelihood estimates

	$t_i = 1$	$t_i = 0$	
$t_j = 1$	(1)	(2)	(7)
$t_j = 0$	(3)	(4)	(8)
	(5)	(6)	(9)

The calculation of EMIM can be simplified, by using the simple maximum likelihood estimates for the probabilities based on the data contained in Table 2.9. Then $I(t_i, t_j)$ is calculated as follows:

$$(1)\log\frac{(1)}{(5)(7)} + (2)\log\frac{(2)}{(6)(7)} + (3)\log\frac{(3)}{(5)(8)} + (4)\log\frac{(4)}{(6)(8)}$$

It can be seen that EMIM is based on co-occurrences data derived from the entire collection. Thus, it is used to measure the dependence between a pair of terms. By having this figure (which correspond to (1)) and knowing the number of documents (9) in the file, thus any inverted file will contain the rest of the frequency data needed to fill in the counts in the other cells. We can get (5) and (7) from the inverted file, which will help determine (2), (3), (4), (6) and (8). In addition, any zero entries in one of the cells 1 to 4 is taken care by letting 0 log 0 = 0.

The construction of the MST, for a given set of n nodes requires the generation of n (n - 1) / 2 EMIM values for distinct pairs of nodes. For example if there are four nodes (a, b, c, d) then six EMIM value will be generated for each pairs of nodes. The algorithm suggested by Whitney (1972) is based on the Dijkstra technique where a maximum spanning tree is grown by successively adjoining the

farthest remaining node to a partially formed tree until all node of the graph are included in the tree.

2.6.2.2 Retrieval Status Value (RSV)

Once the dependence tree has been found, the approximate distribution can be written down in the form of (2.6). t_i and $t_{j(i)}$, now acts as binary selector where if the terms exists in the document it is denoted by 1 and 0 if otherwise. From this, a discriminate function can be derived for the probability of t_i given $t_{j(i)}$, which is as follows:

$$P(t_i \mid t_{j(i)}) = [p_{i|j(i)}^{t_i}(1-p_{i|j(i)})^{1-t_i}]^{t_{j(i)}}[p_i^{t_i}(1-p_i)^{1-t_i}]^{1-t_{j(i)}} \tag{2.7}$$

where $p_{i|j(i)} = P\ (t_i = 1 |\ t_{j(i)} = 1)$ and $p_i = P\ (t_i = 1 |\ t_{j(i)} = 0)$. Then, by substituting (2.7) in (2.6), taking the logarithm and collecting terms, we obtained the Chow Expansion (Chow and Liu, 1968):

$$\begin{aligned}\log P(D) &= \sum_{i=1}^{n}[t_i \log\frac{p_i}{1-p_i}] + \sum_{i=2}^{n}[t_{j(i)} \log\frac{1-p_{i|j(i)}}{1-p_i} + t_i t_{j(i)} \log\frac{p_{i|j(i)}(1-p_i)}{(1-p_{i|j(i)})p_i}] + \sum_{i=1}^{n}\log(1-p_i) \\ &= \sum_{i=1}^{n}[t_i \log\frac{p_i}{1-p_i}] + \sum_{i=2}^{n}[t_{j(i)} \log\frac{1-p_{i|j(i)}}{1-p_i} + t_i t_{j(i)} \log\frac{p_{i|j(i)}(1-p_i)}{(1-p_{i|j(i)})p_i}] + C\end{aligned} \tag{2.8}$$

C represents a constant since it is not associated with any binary selector, hence not included in the calculation of RSV. It is assumed the same for all documents, but varies from query to query. Take note also that if terms are indeed independent, $p_{i|j(i)} = p_i$ and the last two sums in the expansion disappear, leaving the familiar expansion for the independent case. However, since dependence does exist, additional linear and quadric terms are obtained.

As mentioned in section 2.6.1.1, the optimal ranking function is given as *P(R|D) / P(NR|D)*, where *P(R|D)* is the probability of relevant documents whereas *P(NR|D)* refers to the probability of non-relevant documents. Using the *Bayes* theorem expression (2.2) is obtained. It can be rewritten in the manner below. We also have determine that that only *P(D|R)* and *P(D|NR)* is considered as the rest is considered as a constant.

$$\log \frac{P(R \mid D)}{P(NR \mid D)} = \log \frac{P(D \mid R)}{P(D \mid NR)} + \log \frac{P(R)}{P(NR)}$$
$$= \log P(D \mid R) - \log P(D \mid NR) \qquad (2.9)$$

Thus, by adapting the Chow Expansion (2.8) in (2.9), we can determine *P(D|R)* and *P (D|NR)*, which are as follows:

$$\log P(D \mid R) = \sum_{i=1}^{n} [t_i \log \frac{p_i}{1-p_i}] + \sum_{i=2}^{n} [t_{j(i)} \log \frac{1-p_{i|j(i)}}{1-p_i} + t_i t_{j(i)} \log \frac{p_{i|j(i)}(1-p_i)}{(1-p_{i|j(i)})p_i}]$$
$$\log P(D \mid NR) = \sum_{i=1}^{n} [t_i \log \frac{q_i}{1-q_i}] + \sum_{i=2}^{n} [t_{j(i)} \log \frac{1-q_{i|j(i)}}{1-q_i} + t_i t_{j(i)} \log \frac{q_{i|j(i)}(1-q_i)}{(1-q_{i|j(i)})q_i}] \qquad (2.10)$$

where $p_{i|j(i)}$ is the probability of both term t_i and term $t_{j(i)}$ appearing in relevant documents,

p_i is the probability of both term t_i appearing in relevant documents,

$q_{i|j(i)}$ is the probability of both term t_i and term $t_{j(i)}$ appearing in non-relevant documents,

q_i is the probability of both term t_i appearing in non-relevant documents.

Next, by substituting expression (2.9) with (2.10), the complete ranking function is as below. Furthermore, since $P(t_i = 1 \mid t_{j(i)} = 1, R) = P(t_i = 1, t_{j(i)} = 1, R) / P(t_{j(i)} = 1 \mid R)$, hence it further transform the expression into (2.11):

$$\log\frac{P(R\mid D)}{P(NR\mid D)}=\sum_{i=1}^{n}[t_i\log\frac{p_i(1-q_i)}{q_i(1-p_i)}]+\sum_{i=2}^{n}t_{j(i)}[\log\frac{1-p_{i|j(i)}}{1-p_i}-\log\frac{1-q_{i|j(i)}}{1-q_i}]$$
$$+\sum_{i-2}^{n}t_it_{j(i)}[\log\frac{p_{i|j(i)}(1-q_{i|j(i)})}{q_{i|j(i)}(1-p_{i|j(i)})}-\log\frac{p_i(1-q_i)}{q_i(1-p_i)}]$$
$$=\sum_{i=1}^{n}[t_i\log\frac{p_i(1-q_i)}{q_i(1-p_i)}]+\sum_{i=2}^{n}t_{j(i)}[\log\frac{p_{j(i)}-p_{i|j(i)}}{p_{j(i)}(1-p_i)}-\log\frac{q_{j(i)}-q_{i|j(i)}}{q_{j(i)}(1-q_i)}]$$
$$+\sum_{i-2}^{n}t_it_{j(i)}[\log\frac{p_{i|j(i)}(1-q_{i|j(i)})}{q_{i|j(i)}(1-p_{i|j(i)})}-\log\frac{p_i(1-q_i)}{q_i(1-p_i)}-\log\frac{p_{j(i)}(1-q_{j(i)})}{q_{j(i)}(1-p_{j(i)})}] \quad (2.11)$$

2.6.2.3 Probability estimation and improvement

If we already know the set of relevant documents R, then c_i can be interpreted with assistance of the same contingency table used by BIR model (Table 2.8) and thus producing the following assumption. The adjustment factor is also taken in consideration to avoid problem occurring from small value of A and a_i.

a) $p_i = (a_i + 0.5) / (A + 1)$

b) $q_i = (n_i - a_i + 0.5) / (N - A + 1)$

c) $p_{j(i)} = (V_{j(i)} + 0.5) / (A + 1)$

d) $q_{j(i)} = (n_{j(i)} - a_{j(i)} + 0.5) / (N - A + 1)$

e) $p_{i|j(i)} = (a_{i|j(i)} + 0.5) / (A + 1)$

f) $q_{i|j(i)} = (n_{i|j(i)} - a_{i|j(i)} + 0.5) / (N - A + 1)$

where N is the number of documents in database

n_i refers to the frequency of document containing term t_i

$n_{j(i)}$ refers the frequency of document containing term $t_{j(i)}$

$n_{i|j(i)}$ refers to the frequency of document containing both term t_i and term $t_{j(i)}$

A is the total number of relevant documents

a refers to the total number of relevant documents containing a particular term t

On the other hand, if the relevant information is not available, we generally assume that all documents in collection are relevant. Thus, the following assumption is made. q or the distribution of index terms among the non-relevant documents can be approximated by the distribution of index terms t (n) over all the document in the collection (N). It is also assumed that p_i is proportional to q_i, especially $p_i = 1 / (2\text{-}q_i)$ (Robertson and Walker, 1997). The same assumption is also made between $p_{i|j(i)}$ and $q_{i|j(i)}$; and between $p_{j(i)}$ and $q_{j(i)}$. From these assumptions, the Chow Expansion can be adapted into the probabilistic retrieval model without relevance information as follows:

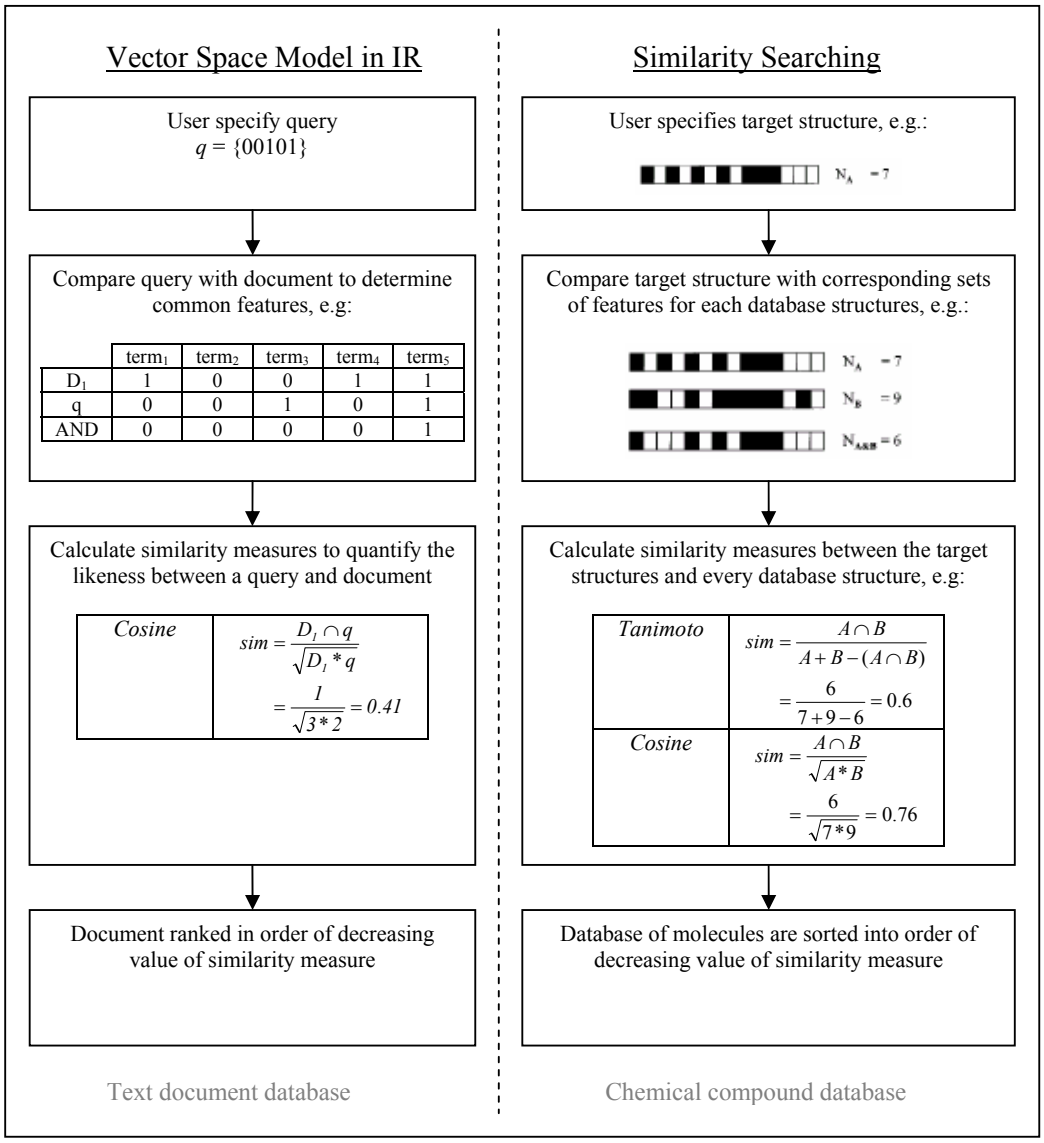
$$\log\frac{P(R\mid D)}{P(NR\mid D)}=\sum_{i=1}^{n}t_i[\log\frac{1}{q_i}]+\sum_{i=2}^{n}t_{j(i)}[\log\frac{q_{j(i)}-q_{i|j(i)}}{q_{j(i)}(1-q_i)}]+\sum_{i-2}^{n}t_i t_{j(i)}[\log\frac{q_i q_{j(i)}}{q_{i|j(i)}}] \qquad (2.12)$$

As a result, documents which contain query terms are retrieved and provided an initial probabilistic ranking for them. Next, probability estimation improvement process is done similar to the BIR model, explained earlier. This process is repeated recursively to improve the estimation on *P(D|R)* and *P(D|NR)* automatically.

2.7 Discussion

Similarity searching as discussed in this chapter compares the query's corresponding set of descriptors to each molecule in the database. A similarity measure is then calculated and based on this numeric value; a ranked list is produced. This similarity searching mechanism can be seen as similar to VSM, as depicted by Figure 2.10. This diagram depicts the industry standard similarity searching process for bit-string based representation. This confirms Willett's (2000) statement that algorithms developed for the processing of textual database are also applicable to processing of chemical structure database and vice versa. This is due to the similarities in the ways that chemical and textual database records are characterised. Text documents are indexed by keywords. Similarly, there are 2D and 3D molecular fragment representations in a chemical database. Each are characterised by some small number of substructural features chosen from a larger number of potential attributes.

As text retrieval system are replacing Boolean retrieval model with best match searching (that is ranking of documents in the decreasing order of similarity to the query), the same can be said with chemical information system. Substructure searching system is now being complemented with similarity searching. Here, similarity measure is calculated to define the inter-molecular structural similarity. Most of the molecular similarity measures used originate from areas outside chemoinformatics, particularly from text retrieval. Similarity coefficients have been used in many fields where classification is important. Classification involves the ordering of objects into groups or sets, on the basis of relationships of similarity that exist between them. It has been used in chemical and textual information retrieval. However, lack of communication between these fields has resulted in much duplication of effort (Ellis, *et al.*, 1994).



	term1	term2	term3	term4	term5
D1	1	0	0	1	1
q	0	0	1	0	1
AND	0	0	0	0	1

$$sim = \frac{D_1 \cap q}{\sqrt{D_1 * q}} = \frac{1}{\sqrt{3*2}} = 0.41$$

$$sim = \frac{A \cap B}{A + B - (A \cap B)} = \frac{6}{7+9-6} = 0.6$$

$$sim = \frac{A \cap B}{\sqrt{A * B}} = \frac{6}{\sqrt{7*9}} = 0.76$$

Figure 2.10 Application of VSM in similarity searching

Similarity searching has inherited the limitations of VSM, the most obvious is assuming that bits are considered as independent of each other, and this in practice is not true. Other than this, it also does not incorporate the importance of a particular fragment in active and inactive known compound that can increase probability of compounds being active or inactive. Hence, PM is proposed. It has a strong theoretical basis and retrieval effectiveness is expected to be near-optimal. Each document's probability of relevance estimate can be reported to the user in ranked output. It would presumably be easier for most users to understand and base their

stopping behaviour upon a probability of relevance than a cosine similarity value. The PM approach has yet to be applied in the compound retrieval system. Hence, to close the knowledge gap, these alternatives of information retrieval in compound similarity searching, need to be taken up, and determine whether PM is better in terms of retrieving structures from chemical databases.

2.8 Summary

In this chapter, we have discussed important fundamentals of IR and chemical retrieval system. Just as a document is relevant or not to a particular user's query, so is a molecule active or inactive, in some particular biological test. Similarity in text and chemical database particularly in representation of records, has allow application of algorithms for processing textual databases to processing chemical structure. For this project, it is in terms of applying PM in similarity searching, mainly the BIR model and BD model. Other than that, we also discussed about the important elements in calculating similarity measures. There are molecular representation and similarity coefficient to quantify the similarity between the representations of two molecules. In the next chapter, details the real implementation of the proposed approach in the chemical database environment. Project methodology covers the experimental designs as well as data and equipment used in this project.

CHAPTER 3

METHODOLOGY

In the previous chapter, we have discussed on the chemical compound similarity searching as well as the IR models in detail. The chapter also covers how both of these fields are related with each other. As the objective of this project is to apply the Probability Model in chemical compound similarity searching, hence there is a need to investigate whether the proposed approach yields better performance of screening chemical compounds compared to the existing method. This chapter discusses about the steps taken to carry out this research. It mainly focuses on the computational experiment designs (Figure 3.1) where it details about the data set, structural descriptors and similarity searching methods used. Evaluation is also done to analyse the performance of each of the similarity searching methods.

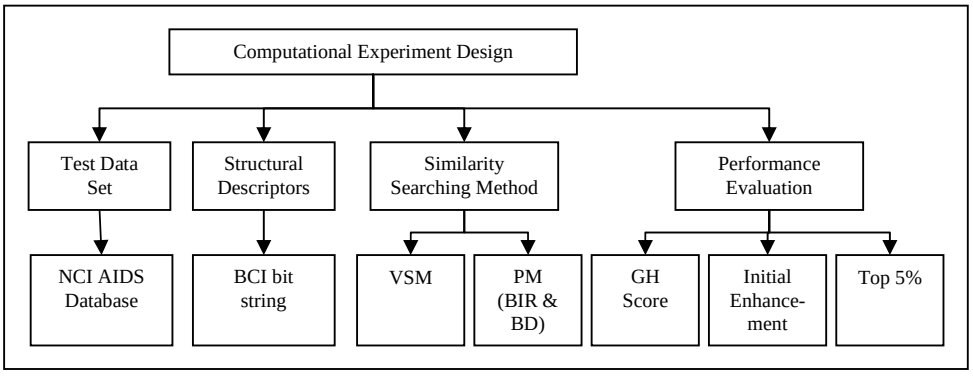


Figure 3.1 Outline of Chapter 3

3.1 Computational Experiment Design

The basis of this study comes from the virtual screening environment itself. In a similarity search of a corporate database, a known bioactive compound is used as a target structure to prioritise molecules for biological screening. An effective similarity method will give a high percentage of actives among those compounds ranked highest in terms of structural similarity with that target. As the similarity values decreases, the percentage of actives covered will become gradually less. This is because more and more dissimilar molecules are used, with no actives covered when the compounds and the active target have no structural similarity between them.

Figure 3.2 depicts the work flow of the computational experiment of this project. Using the NCI AIDS dataset as the test data set, all chemical structures are firstly represented using the BCI bit string. Then, a series of *simulated similarity searching* studies is conducted to compare the effectiveness of different similarity methods. In the data set, each active compound acts as a probe to search the remainder of the data set. Compounds are then ranked according to the calculated similarity values, from most to least similar. Lastly, the ranked list is analyzed to determine which method is better. In doing so, we need to consider an important criterion, which is: how good are the methods in separating active and inactive structures? (Sheridan and Kearsley, 2002). It is not the absolute similarity value that determines which method is better because it is generally not comparable between methods. Hence, three approaches in evaluating the performance of the search methods are taken up, mainly the GH score, initial enhancement and the number of actives at top 5% of ranked list. Details of this approaches is explained in the following sections.

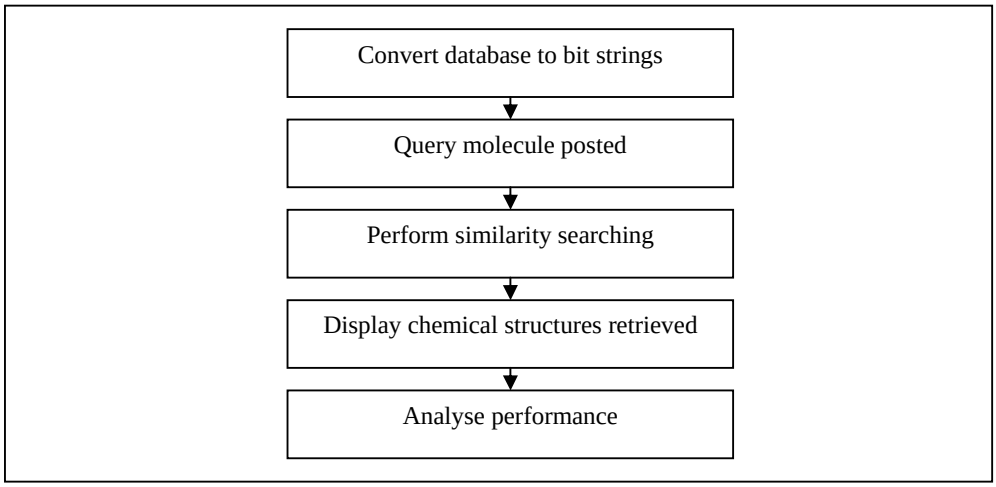


Figure 3.2 Workflow of the simulated similarity searching.

3.2 Test Data Sets

Evaluating the performance of different similarity measures requires an ideal test data set that satisfies the following requirement (Chen and Reynolds, 2002) that is it should sample the chemical regions it covers as thoroughly as possible so that it can really test the capability of a similarity measure to differentiate between active and inactive structure.

The experiment here uses the National Cancer Institute (NCI) AIDS Database (National Cancer Institute, 1999) as the test data set to satisfy this requirement. It represents a large data set composed of both active and inactive compounds against a specific therapeutic target and provides a thorough sampling of a particular region in chemical space. This public database contains 5772 compounds, including 247 confirmed active (CA), 802 confirmed moderately active (CM) and 4723 confirmed inactive (CI). In this data set, both the CA and CM are treated equally as actives and the CI as inactive. The following shows the format of the input file for the dataset as well as some sample data:

{compound name}	*{A list of bits set to 1 in the bit string}*	*{Separator}*	*{Total bits set to 1}*
aids99_CA_STR1	1 3 6 8 19 77 80 81 99 103 . . .	0	117
aids99_CM_STR10	1 6 8 39 46 86 89 149 242 298 . . .	0	53
aids99_CI_STR100	1 2 3 6 8 14 16 38 40 45 . . .	0	72

Figure 3.3 File format of data set with sample data (aids99_5772.bci1052.txt)

The above data set file can also be used to generate an inverted file. Inverted file consist of a list of molecule IDs containing fragments. It is mostly used in this work, to determine total number of structures that contains a particular bit b_i, where i refers to the location of the bit b in the bit string. This is also known as the notation n_i, mostly used in the BIR and BD model. The following shows the format of the inverted file created based on the dataset, together with some sample data:

{Bit number}	*{A list of structures containing bit b_i}*	*{Separator}*	*{Total structures containing bit b_i }*
1	1 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17. . .	0	4663
2	2 4 5 7 8 9 17 24 28 34 38 39 40 49 50 . . .	0	2986
3	1 3 5 7 8 9 10 11 12 13 14 15 16 17 18. . .	0	3487

Figure 3.4 File format of inverted file with sample data (inverted.txt)

3.3 Structural Descriptors

A chemical structure in this work is represented using BCI (Barnard Chemical Information Ltd.) bit string. A molecule is divided into fragments of specific functional groups or substructures. The fragments are recorded in a predefined fragment dictionary that specifies the corresponding bit positions of the fragments in the bit string. Bits represent the absence or presence of fragments either individually or as a group. The following figure shows an example of a simple bit

string. Here, the dictionary contains four fragments; each corresponds to an individual position in the fingerprint bit string.

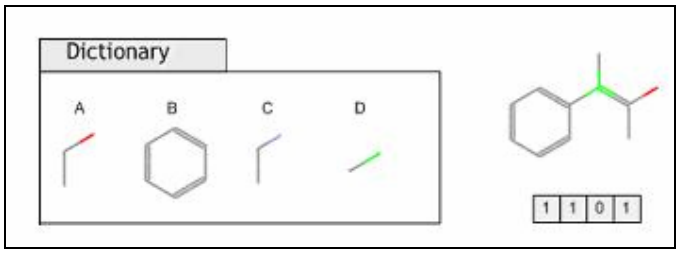


Figure 3.5 Example of simple fingerprint (Barnard Chemical Information Ltd.)

This project however uses the BCI 1052-bit structural key-based bit string. It is generated based on the presence or absence of fragments in the BCI's standard 1052 fragments-dictionary. It encodes augmented atoms, atom pairs with a distance between atoms of any length desired, atom sequences of any length desired; ring composition sequences for any size desired and ring fusion descriptors.

Generating descriptors for this project is a simple procedure where scanning through the data set (Figure 3.3) there is a list of bit number that is set to '1' in the bit string of a particular chemical structure. Using this list, the bit strings are then generated. The following are some sample of descriptors generated:

{compound name}	*{Bit string representation}*
aids99_CA_STR1	10100101000000000010000000000000000000000000000000000000 . . .
aids99_CM_STR10	10000101000000000000000000000000000000010000010000000000 . . .
aids99_CI_STR100	11100101000001010000000000000000000001010000100000100000 . . .

Figure 3.6 Example of descriptors generated (aids.txt)

3.4 Experiment 1: Comparing the Effectiveness of Similarity Searching Methods

This project deals with three similarity searching methods. The first is the existing approach in similarity searching which is based on the VSM. Here, the *Tanimoto* coefficient is used as the similarity measure. The second approach involves applying the PM in similarity searching. There are two models that are used here namely the Binary Independence Retrieval (BIR) and Binary Dependence (BD) Model. According to Losee (1994), BD model has actually improved the performance of retrieval system compared to those applying independence assumptions of terms. Even though, it is theoretically stronger than the BIR model, its performance is yet to be proven in the chemical compound database.

3.4.1 Vector Space Model

As explained in the literature review, the industry standard similarity searching process for bit-string based representation consists of the following steps. First, specify the specification of an entire target structure. Then, compare the target structure with corresponding set of features for each database structure. Each comparison enables the calculation of a measure of similarity. In order to do so, the *Tanimoto* coefficient is used. Hence, the measure of similarity between a compound structure *A* and *B* is defined as follows:

$$sim(A, B) = \frac{c}{a + b - c}$$

where *a* is the number of unique fragments in compound *A*,

b is the number of unique fragments in compound *B*,

c is the number of unique fragments shared by compounds *A* and *B*.

It is chosen because it is the standard for measuring the binary structural similarity of compounds and it has one of the best overall performances compared to other coefficients (Salim, 2002). Finally, the retrieval system ranks structures based on their similarity to the target structure. They are sorted into order of decreasing value of similarity measure. Figure 3.7 details the algorithm of this similarity method.

1. Post active structure as query
2. For every structure in database
   2.1. common = 0
   2.2. For all structure screen, i
      2.2.1. if query.screen[i] = '1' and structure.screen[i] = '1'
             common = common +1
   2.3. Calculate similarity
      2.3.1. *a* = total bits set to 1 for query
      2.3.2. *b* = total bits set to 1 for structure
      2.3.3. *c* = common
      2.3.4. *tanimoto* = *c* / (*a* +*b*-*c*)
3. Rank structures in decreasing order of *Tanimoto* scores

Figure 3.7 Algorithm of existing similarity searching method

3.4.2 Binary Independence Retrieval Model

A chemical compound structure is represented using the binary indexing concept. To apply BIR model, bits of a chemical structure *S* are map onto disjoint concept by forming conjuncts of all bit *b*, in which each bit occurs either positively or negated, that is:

$$S = b_1^{\alpha_1} \cap \ldots \cap b_n^{\alpha_n} \quad \text{with} \quad b_i^{\alpha_i} = \begin{cases} b_i \text{ if } \alpha_i = 1 \\ \overline{b_i} \text{ if } \alpha_i = 0 \end{cases}$$

where b_i refers to bit b at location i on the bit string,

α_i acts as binary selector. If is $\alpha_i = 1$, then the bit occurs in the structure, otherwise it is 0 and assumed negated.

In order to estimate the ranking score of a particular structure against the target structure or query, the optimal similarity function is the ratio of probability of active structures ($P(A|S)$) to probability of inactive structures ($P(NA|S)$). This is also referred to as the *Retrieval Status Value* (RSV). Based on the Bayes theorem, the similarity function becomes the following:

$$\frac{P(A \mid S)}{P(NA \mid S)} = \frac{P(A) \cdot P(S \mid A)}{P(NA) \cdot P(S \mid NA)} \tag{3.1}$$

where $P(S|A)$ is the probability of an active structure,

$P(S|NA)$ is the probability of an inactive structure,

$P(A)$ is the probability of actives,

$P(NA)$ is the probability of inactives.

However, we need to associate the relevance of a structure to an explicit feature. Two variables are used which are p_i (probability that bit b_i appearing in an active structure) and q_i (probability that bit b_i appearing in an inactive structure). Hence, we get the following expression of $P(S|A)$ and $P(S|NA)$:

$$\begin{aligned} P(S \mid A) &= \prod_{i=1..n} (p_i)^{\alpha_i} (1 - p_i)^{1-\alpha_i} \\ P(S \mid NA) &= \prod_{i=1..n} (q_i)^{\alpha_i} (1 - q_i)^{1-\alpha_i} \end{aligned} \tag{3.2}$$

Then, by substituting (3.2) in (3.1) and taking logs of the ranking function, it will turn into a linear discriminate function as stated below:

$$\frac{P(A \mid S)}{P(NA \mid S)} = \sum_{i=1}^{n} \alpha_i \log\left(\frac{p_i(1-q_i)}{q_i(1-p_i)}\right) + \log\left(\frac{1-p_i}{1-q_i}\right) + \log\frac{P(A)}{P(NA)}$$

$$= \sum_{i=1}^{n} c_i \alpha_i + C$$

$$= \sum_{b_i \in S \cap q} c_i \alpha_i$$

where c_i indicates the capability of bit b_i to discriminate active from inactive structure. It is the only term considered here as it is associated with the binary selector α_i. Constant C is ignored because it is the same for all structures, hence having no effect on the expression. In addition, it is assumed that $p_i = q_i$ for all terms not included in the query formulation (Fuhr, 1992). This restricts the evaluation of the sum to query bits and thus producing the above expression.

In a chemical compound database, the activity and inactivity of a particular structure is already determined. Hence we can estimate the probabilities *P (S|A)* and *P (S|NA)* based on the contingency table in Table 3.1:

Table 3.1: Contingency table of relevance judgement (van Rijsbergen, 1979)

	Active	Inactive	
$\alpha_i = 1$	*a*	*n-a*	*n*
$\alpha_i = 0$	*A-a*	*N-n-A+a*	*N-n*
	A	*N-A*	*N*

Here, *N* is the total number of structures in the database, *n* refers to the total number of structures which contain bit b_i, *A* is the total the total number of active structures, and *a* refers to the total number of active structures containing bit b_i. From this table, the following is estimated:

a) $p_i = a_i / A$

b) $q_i = (n_i - a_i) / (N - A)$

Hence, the c_i can be rewritten as:

$$c_i = \log \frac{a(N - A - n + a)}{(n - a)(A - a)}$$

However, the formulas of p_i and q_i may pose problems for small values of A and a_i. To avoid these problems, an adjustment factor is added which yields:

a) $p_i = (a_i + 0.5) / (A + 1)$

b) $q_i = (n_i - a_i + 0.5) / (N - A + 1)$

Figure 3.8 summarizes the algorithm of this similarity searching method.

1. Post active structure as query
2. N = Total number of structures in database
3. A = Total number of active structures in database
4. Determine a_i
   - 4.1. For each screen i
     - 4.1.1. a_i = Total number of structures which is a subset of A containing bit b_i
5. For every structure in the database
   - 5.1. Calculate similarity
     - 5.1.1. RSV = 0.0
     - 5.1.2. For every common bit shared by both query and structure
       - 5.1.2.1. $p_i = (a_i + 0.5) / (A + 1)$
       - 5.1.2.2. $q_i = (n_i - a_i + 0.5) / (N - A + 1)$
       - 5.1.2.3. RSV = RSV + log10 $(p_i / (1- p_i))$ + log10 $((1- q_i) / q_i)$
6. Rank structures in decreasing order of their RSV

Figure 3.8 BIR model algorithm

3.4.3 Binary Dependence Model

Bit dependencies refer to the presence or absence of a bit which provides information about the probability of presence or absence of another bit. Assume vector structure, $S = \{b_1, b_2 \ldots b_n\}$ are binary values. It is arbitrarily complex to capture all dependence data as we need to condition each variable in turn on a steadily increasing set of other variable. Hence, to estimate probability of a structure ($P(S)$) this model captures only the significant pairwise dependence information. Thus $P(S)$ is the probability of a bit i solely dependent on some preceding bit $b_{j(i)}$:

$$P(S) = \prod_{i=1}^{n} P(b_i \mid b_{j(i)}) \qquad 0 \le j(i) \le i \tag{3.4}$$

A probability distribution that can be represented as in the above expression is called a probability distribution of first-order tree dependence (Chow and Liu, 1968). Take for example the following dependence tree:

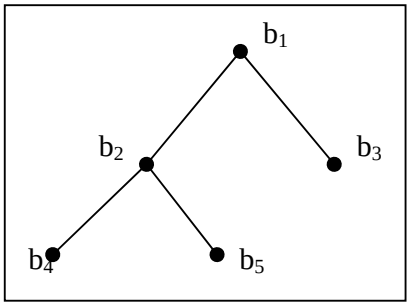


Figure 3.9 A dependence tree

From equation (3.4), the probability of a structure can be written as $P(b_1)P(b_2|b_1)\ P(b_3|b_1)\ P(b_4|b_2)\ P(b_5|b_2)$, or the following product expansion:

$$P(b_1)P(b_2|b_{j(2)})\ P(b_3|b_{j(3)}) \ldots\ P(b_n|b_{j(n)})$$

where the function $j(i)$ exhibits the limited dependence of one bit on preceding bits.

There are many possible dependence tree that can be generated to find the best ordering and mapping of *j(i)*. Chow and Liu (1968) suggest constructing a *Maximum Spanning Tree* (MST) using the *Expected Mutual Information Measure* (EMIM). EMIM is a measure of a variable containing the information about another variable. Hence, it requires the counting of co-occurrences of bits in a structure, and thus used to measure the dependence between a pair of bits.

Let *G(V,E)* be a connected graph, where *V* is the set of nodes and *E* is the set of edges. Assign to each edge *(i, j(i))* a weight $w_{(i, j(i))}$ obtained from calculating the EMIM value of the pair of variable. An MST is a tree that includes every node and has maximal total weight. It simply maximizes the sum:

$$\sum_{i,j} I(b_i, b_{j(i)})$$

where $I(b_i, b_{j(i)})$ represents the expected mutual information between bit b_i and $b_{j(i)}$,

$$I(b_i, b_{j(i)}) = \sum_{b_i, b_{j(i)}} P(b_i, b_{j(i)}) \log \frac{P(b_i, b_{j(i)})}{P(b_i) P(b_{j(i)})}$$

The contingency table below further simplify the calculation of EMIM in to the following:

$$I(b_i, b_{j(i)}) = (1) \log \frac{(1)}{(5)(7)} + (2) \log \frac{(2)}{(6)(7)} + (3) \log \frac{(3)}{(5)(8)} + (4) \log \frac{(4)}{(6)(8)}$$

Table 3.2: Contingency table of maximum likelihood estimates

	$b_i = 1$	$b_i = 0$	
$b_{j(i)} = 1$	(1)	(2)	(7)
$b_{j(i)} = 0$	(3)	(4)	(8)
	(5)	(6)	(9)

Hence, the first step in this model is to generate the MST to identify the most important pairwise dependencies. Each given chemical structure collection will

construct an MST based on all bits included in the collection. There are many algorithms in generating an MST from pairwise association measures. The most efficient is by Whitney (1972). It is based on the *Dijkstra* technique where a maximum spanning tree is grown by successively adjoining the farthest remaining node to a partially formed tree until all node of the graph are included in the tree (Figure 3.10).

1. To initialise:
   1.1. Start with graph $G_0 = (V_0, E_0)$ consisting of a single solved node.
   1.2. The arc set is empty.
2. Find all unsolved nodes that are directly connected by a single arc to any solved node *(i, j(i))*. For each unsolved node, calculate the weight $w_{(i, j(i))}$ based on the EMIM value .
3. Choose the largest value of EMIM and add the corresponding unsolved node to the solved set. Also add the corresponding edge to the arc set.
4. If the newly solved node is not the destination node then repeat the process again.

Figure 3.10 The Dijkstra algorithm

Figure 3.11 further summarises the algorithm for constructing the dependence tree in this work. At each iterative step, the unsolved nodes are stored in array *not_in_tree*. The node of the partially completed tree with the largest value of EMIM to node *not_in_tree[i]* is stored in the array *farthest_existing_node[i]* and the length or weight of edge from *not_in_tree[i]* to *farthest_existing_node[i]* is stored in *biggest_edges[i]*. Hence, the node not yet in the tree which is farthest to a node of the tree may be found by searching for the maximal element of array *biggest_edge*. It is then added to the tree and removed from array *not_in_tree*. For each remaining in array *not_in_tree*, the distance from farthest node of the tree (stored in *biggest_edge*) is compared to the distance from the new node of the tree. Then the array *biggest_edge* and *farthest_existing_node* is updated if the new distance is farther. This process is repeated until all nodes are in the tree.

1. Calculate EMIM
   1.1. For (i = 0; i< MAXSCREENS, i++)
      1.1.1. For (j = i ; j< MAXSCREENS, j++)
         1.1.1.1. Calculate EMIM for bit *i* and bit *j* and stored in array DM[i][j]
         1.1.1.2. DM[i][j] = DM[j][i]
2. Initialise the following:
   2.1. num_nodes_outside = MAXSCREENS-1
   2.2. new_node = MAXSCREENS-1
   2.3. num_of_edges = 0
   2.4. for *i* = 0 to *i* < num_nodes_outside
      2.4.1. not_in_tree[*i*] = *i*
      2.4.2. biggest_edges[*i*] = DM[*i*][new_node]
      2.4.3. farthest_existing_node[*i*] = new_node
3. Update labels of nodes not yet in tree
   3.1. for *i* = 0 to *i* < num_nodes_outside
      3.1.1. outside node = not_in_tree[*i*]
      3.1.2. edge weight = DM[outside node][new_node]
      3.1.3. if (biggest_edges[*i*] < edge weight)
         biggest_edges[*i*] = edge weight
         farthest_existing_node[*i*] = new_node
4. Find node outside tree farthest from tree
   4.1. best edge = biggest_edges[0]
   4.2. for *i* = 0 to *i* < num_nodes_outside
      4.2.1. if (biggest_edges[*i*] > best edge)
         best edge = biggest_edges[*i*]
         best node = *i*
   4.3. MST[num_of_edges][0] = not_in_tree[best node]
   4.4. MST[num_of_edges][1] = farthest_existing_node[best node]
   4.5. new_node = not_in_tree[best node]
   4.6. num_of_edges = num_of_edges + 1
5. Delete new tree node from array not_in_tree
   5.1. biggest_edges[best node] = biggest_edges[num_nodes_outside - 1]
   5.2. not_in_tree[best node] = not_in_tree[num_nodes_outside - 1]
   5.3. farthest_existing_node[best node] = closet_existing_node [num_nodes_outside - 1]
   5.4. num_nodes_outside = num_nodes_outside -1
6. Repeat Step 3 to 5 until num_nodes_outside = 0

Figure 3.11 The MST construction algorithm

Next, the dependence tree is then used to expand the query by taking the original query bits and adding all bits that are immediately adjacent in the MST. The pairwise term dependencies obtained for all bit pairs b_i and b_j in the expanded query such that each pair (b_i, b_j) is represented by an edge in the spanning tree.

The following explains the similarity function or RSV of this model. As mentioned in section 3.4.2, the similarity function is as stated in expression (3.1). Based also the discussion in this section, we have found that only the term *P(S|A)* and *P(S|NA)* are considered. The rest remains as a constant and does not include in the calculation of RSV. Hence obtaining the expression:

$$\frac{P(A \mid S)}{P(NA \mid S)} = \log P(S \mid A) - \log P(S \mid NA) \tag{3.5}$$

For each structure *S*, the factors *P(S|A)* and *P(S|NA)* are computed using the following expression:

$$\log P(S \mid A) = \sum_{i=1}^{n} [b_i \log \frac{p_i}{1-p_i}] + \sum_{i=2}^{n} [b_{j(i)} \log \frac{1-p_{i \mid j(i)}}{1-p_i} + b_i b_{j(i)} \log \frac{p_{i \mid j(i)}(1-p_i)}{(1-p_{i \mid j(i)})p_i}] + C$$

$$\log P(S \mid NA) = \sum_{i=1}^{n} [b_i \log \frac{q_i}{1-q_i}] + \sum_{i=2}^{n} [b_{j(i)} \log \frac{1-q_{i \mid j(i)}}{1-q_i} + b_i b_{j(i)} \log \frac{q_{i \mid j(i)}(1-q_i)}{(1-q_{i \mid j(i)})q_i}] + C \tag{3.6}$$

where b_i refers to bit *b* at location *i*,

$b_{j(i)}$ refers to bit *b* at location *j(i)* where bit $b_{j(i)}$ is the preceding bit of bit b_i,

$p_{i|j(i)}$ is the probability of both bit b_i and bit $b_{j(i)}$ appearing in active structures,

p_i is the probability of both bit b_i appearing in active structures,

$q_{i|j(i)}$ is the probability of both bit b_i and bit $b_{j(i)}$ appearing in inactive structures,

q_i is the probability of both bit b_i appearing in inactive structures,

Then, by substituting (3.6) in (3.5), and taking into account that $P(b_i = 1 \mid b_{j(i)} = 1, A) = P(b_i = 1, b_{j(i)} = 1, A) / P(b_{j(i)} = 1 \mid A)$, hence it further transform the expression into the following:

$$\frac{P(A \mid S)}{P(NA \mid S)} = \sum_{i=1}^{n} [b_i \log \frac{p_i(1-q_i)}{q_i(1-p_i)}] + \sum_{i=2}^{n} b_{j(i)} [\log \frac{p_{j(i)} - p_{i|j(i)}}{p_{j(i)}(1-p_i)} - \log \frac{q_{j(i)} - q_{i|j(i)}}{q_{j(i)}(1-q_i)}]$$
$$+ \sum_{i-2}^{n} b_i b_{j(i)} [\log \frac{p_{i|j(i)}(1-q_{i|j(i)})}{q_{i|j(i)}(1-p_{i|j(i)})} - \log \frac{p_i(1-q_i)}{q_i(1-p_i)} - \log \frac{p_{j(i)}(1-q_{j(i)})}{q_{j(i)}(1-p_{j(i)})}] \tag{3.7}$$

Relevance information is available in the database, this model computes the probability of $P(S|A)$ and $P(S|NA)$ using the same contingency table as the BIR model (Table 3.1) and thus producing the following assumption. The adjustment factor is also taken in consideration to avoid problem occurring from small value of A and a_i.

a) $p_i = (a_i + 0.5) / (A + 1)$

b) $q_i = (n_i - a_i + 0.5) / (N - A + 1)$

c) $p_{j(i)} = (V_{j(i)} + 0.5) / (A + 1)$

d) $q_{j(i)} = (n_{j(i)} - a_{j(i)} + 0.5) / (N - A + 1)$

e) $p_{i|j(i)} = (a_{i|j(i)} + 0.5) / (A + 1)$

f) $q_{i|j(i)} = (n_{i|j(i)} - a_{i|j(i)} + 0.5) / (N - A + 1)$

where
- N is the number of structures in database
- n_i refers to the frequency of structure containing bit b_i
- $n_{j(i)}$ refers the frequency of structure containing bit $b_{j(i)}$
- $n_{i|j(i)}$ refers to the frequency of structure containing both bit b_i and bit $b_{j(i)}$
- A is the total number of active structures
- a refers to the total number of active structures containing a particular bit b

Figure 3.12 summarizes the algorithm of this similarity searching method.

1. Create dependence tree for collection
2. Post active structure as query
3. Expand query by taking the original query terms and adding all terms that are immediately adjacent in the dependence tree.
4. N = Total number of structures in database
5. A = Total number of active structures in database
6. Determine a
   - 6.1. For each screen i
     - 6.1.1. a_i = Total of structures which is a subset of A containing bit b_i
   - 6.2. For each pair in expanded query
     - 6.2.1. $a_{i|j(i)}$ = Total of structures which is a subset of A containing both bit b_i and $b_{j(i)}$
7. For every structures in database
   - 7.1. RSV = 0.0
   - 7.2. Calculate similarity
     - 7.2.1. For every common bit shared by both query and structure
       - 7.2.1.1. $p_i = (a_i + 0.5) / (A + 1)$
       - 7.2.1.2. $q_i = (n_i - a_i + 0.5) / (N - A + 1)$
       - 7.2.1.3. RSV = RSV + $(p_i*(1-q_i))/(q_i*(1-p_i))$
       - 7.2.1.4. Find parent of matched bit in dependence tree. If found and appear in structure bit string then
         $p_{j(i)} = (a_{j(i)} + 0.5) / (A + 1)$, $q_{j(i)} = (n_{j(i)} - a_{j(i)} + 0.5) / (N - A + 1)$
         $p_{i|j(i)} = (a_{i|j(i)} + 0.5) / (A + 1)$, $q_{i|j(i)} = (n_{i|j(i)} - a_{i|j(i)} + 0.5) / (N - A + 1)$
         $b = ((p_{j(i)}-p_{i|j(i)})/(p_{j(i)}*(1-p_i))) - ((q_{j(i)}-q_{i|j(i)})/(q_{j(i)}*(1-q_i)))$
         $c = ((p_{i|j(i)}*(1-q_{i|j(i)}))/(q_{i|j(i)}*(1-p_{i|j(i)}))) - ((p_i*(1-q_i))/(q_i*(1-p_i))) - ((p_{j(i)}*(1-q_{j(i)}))/(q_{j(i)}*(1-p_{j(i)})))$
         RSV = RSV + b + c
8. Rank structures in decreasing order of their RSV

Figure 3.12 BD model algorithm

3.4.4 Performance Evaluation

Performance of each approach is evaluated by computing the following. Analysis on the result will be made and comparison among them will be done to determine which approach fairs well in the chemical compound database.

a) *GH Score* (Güner, 1998)

The *GH score* gives an indication of how good the retrieved list is with respect to a compromise between maximum yield and maximum percent of actives retrieved. Consider the following:

D is the number of chemical structures in the database,

A is the number of actives structures in the database,

H_t is the number of structures in a retrieved list, and

H_a is the number of active structures in a retrieved list.

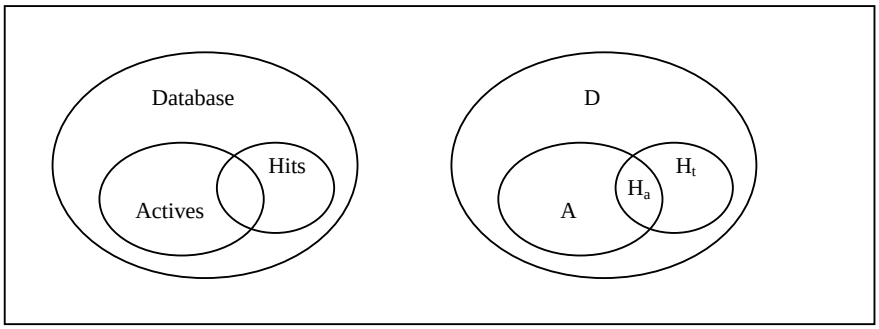


Figure 3.13 Schematic representation of the chemical database space, actives and hit (retrieved compound) list (Güner, 1998).

The different metrics that can be used to evaluate the quality of a hit list are given below:

- The percent yield of actives or also referred to as proportion of structures retrieved that are active (Precision).

$$\%Y = \frac{H_a}{H_t} \times 100$$

- Percent ratio of the actives in the list or also referred to as proportion of active structures that are retrieved (Recall).

$$\%A = \frac{H_a}{A} \times 100$$

- Number of actives not in the hit list:

$$False\ negative = A - H_a$$

- Number of inactive structures in the hit list:

$$False\ positive = H_t - H_a$$

Thus, the GH score is actually the sum of yield and ratio of actives in the hit list. It is then divided by two, as denoted below:

$$GH = \frac{Y + A}{2} = \frac{\left(\frac{H_a}{H_t}\right) + \left(\frac{H_a}{A}\right)}{2} = \frac{H_a(A + H_t)}{2AH_t}$$

b) Initial enhancement, which refers to a number of chemical structure retrieved before half of the actives are found. The less the value, the better the performance of the similarity searching system.

c) The number of actives at top 5% of the list. If there are quite a number of active structures on the top 5% of this list, it denotes a good similarity searching system.

3.5 Experiment 2: Comparing the Query Fusion Result of Similarity Searching Methods

The purpose of this experiment is to investigate whether query fusion result of the proposed probability models, is better than VSM. Data fusion is an approach where data, evidence, or decisions coming from or based on multiple sources, about the same set of objects are integrated to increase the quality of decision making under uncertainty about the objects (Salim, 2002). The advantage of this approach is that it can improve confidence in decisions with the use of complementary information by inferring information that is outside of the capability of a single sensor information.

IR systems apply data fusion in combining the following components: multiple document representations, multiple queries and multiple retrieval techniques. This section focuses on data fusion in combining multiple queries (Belkin *et. al.,* 1995). A number of studies have looked into the effect of capturing multiple queries from a single searcher or multiple searchers given the same specification of an information need, to get more evidence about relevance. Some retrieval models were proposed that incorporates multiple representation of the information need (Turtle and Croft, 1991; Rajashekar and Croft, 1995). Belkin *et. al.* (1995) on the other hand, found that applying adaptive weighting schemes to query combination gives better result than best individual system where progressive result combination were taken into consideration.

In chemoinformatic, query combination is also being applied in combining several molecules in a single query. Similarity searches using mixtures as queries and/or database entries was found to give better or at least equal results to experiments using single compounds as targets and database entries (Sheridan, 2000). Combined chemical target has also been used in an iterative similarity searching using approach analogous to relevance feedback in the text retrieval area (Singh *et. al.*, 2001). Hence, based on this concept, this second experiment uses combined chemical target in an iterative similarity searching to estimating probability instead of obtaining from the entire collection.

The NCI AIDS dataset is divided equally to four sets, with 1443 structures in each set. The NCI AIDS dataset organises compounds according to the following: CA, CM and CI. Hence, this simplifies the division of the data sets with each set having equal distribution of CA, CM and CI. The algorithm of this process is shown in Figure 3.14 and the result of this division is shown in Table 3.3.

```
1. Set No = 1
2. For every structure in database
   2.1. Read compound name and its screen from Aids.txt (NCI AIDS dataset)
   2.2. Separate into four equal sets
      2.2.1. If Set No =1
             Store name and screen in the first file set.
             Set No = Set No + 1
      2.2.2. If Set No =2
             Store name and screen in the second file set.
             Set No = Set No + 1
      2.2.3. If Set No = 3
             Store name and screen in the third file set.
             Set No = Set No + 1
      2.2.4. If Set No = 4
             Store name and screen in the fourth file set.
             Set No = 1
```

Figure 3.14 Algorithm for the division of NCI AIDS dataset into four equal sets

Table 3.3: The content of the four equal sets of dataset

	Total no. of CA	Total no. of CM	Total no. of CI
Set No 1	62	201	1180
Set No 2	62	200	1181
Set No 3	62	200	1181
Set No 4	61	201	1181
Total Structures	**247**	**802**	**4723**

Next, an active compound is posted as query. The similarity searching is conducted on the first set and it returns the top 100 compounds. Based on these compounds, the probability of p_i and q_i for each bit i is computed. It will then be used to obtained the ranking score function (RSV) for the second set. The same procedure is repeated again, where the probability of p_i and q_i obtained from the top 100 compounds of the second set is used to compute the RSV for the third set. Finally, the probability of p_i and q_i obtained from the top 100 compounds of the third set is used to compute the RSV for the fourth and final set. Thus, the result of each query posted will return a total number of 400 compounds obtained by combining the result of each set.

3.5.1 Binary Independence Retrieval Model

Figure 3.15 summarizes the algorithm of this similarity searching method.

1. Separate datasets in 4 equally divided sets
2. Post active structure as query
3. N = Total number of structures in set
4. Conduct similarity searching on first set using the BIR model
   - 4.1. A = Total number of active structures in first set
   - 4.2. Determine a_i
     - 4.2.1. For each screen i
       - 4.2.1.1. a_i = Total number of structures which is a subset of A containing bit b_i
   - 4.3. Calculate similarity for every structure in the first set
     - 4.3.1. RSV = 0.0
     - 4.3.2. For every common bit shared by both query and structure
       - 4.3.2.1. $p_i = (a_i + 0.5) / (A + 1)$
       - 4.3.2.2. $q_i = (n_i – a_i + 0.5) / (N – A + 1)$
       - 4.3.2.3. RSV = RSV + log10 $(p_i / (1- p_i))$ + log10 $((1- q_i) / q_i)$
   - 4.4. Rank structures in decreasing order of their RSV
5. Retrieve top 100 compounds from the ranked list and obtain the following
   - 5.1. V = Total number of active structures in the top 100
   - 5.2. Determine V_i
     - 5.2.1. For each screen i
       - 5.2.1.1. V_i = Total number of structures which is a subset of V containing bit b_i
   - 5.3. Calculate similarity for every structure in the next set
     - 5.3.1. RSV = 0.0
     - 5.3.2. For every common bit shared by both query and structure
       - 5.3.2.1. $p_i = (V_i + 0.5) / (V + 1)$
       - 5.3.2.2. $q_i = (n_i – V_i + 0.5) / (N – V + 1)$
       - 5.3.2.3. RSV = RSV + log10 $(p_i / (1- p_i))$ + log10 $((1- q_i) / q_i)$
   - 5.4. Rank structures in decreasing order of their RSV
6. Repeat step 5 for set 3 and 4.

Figure 3.15 BIR model query combinational algorithm

3.5.2 Binary Dependence Model

Figure 3.16 summarizes the algorithm of this similarity searching method.

1. Separate datasets in 4 equally divided sets
2. Post active structure as query
3. N = Total number of structures in set
4. Conduct similarity searching on first set using the BD model
   - 4.1. Load dependence tree for set and expand query.
   - 4.2. A = Total number of active structures in set
   - 4.3. Determine V
     - 4.3.1. For each screen i
       - 4.3.1.1. a_i = Total of structures which is a subset of A containing bit b_i
     - 4.3.2. For each pair in expanded query
       - 4.3.2.1. $a_{i|j(i)}$ = Total of structures which is a subset of A containing both bit b_i and $b_{j(i)}$
   - 4.4. Calculate similarity for every structures in first set
     - 4.4.1. RSV = 0.0
     - 4.4.2. For every common bit shared by both query and structure
       - 4.4.2.1. $p_i = (a_i + 0.5) / (A + 1)$
       - 4.4.2.2. $q_i = (n_i - a_i + 0.5) / (N - A + 1)$
       - *4.4.2.3.* RSV = RSV + $(p_i*(1-q_i))/(q_i*(1-p_i))$
       - 4.4.2.4. Find parent of matched bit in dependence tree. If found and appear in structure bit string then

         $p_{j(i)} = (a_{j(i)} + 0.5) / (A + 1)$, $q_{j(i)} = (n_{j(i)} - a_{j(i)} + 0.5) / (N - A + 1)$

         $p_{i|j(i)} = (a_{i|j(i)} + 0.5) / (A + 1)$, $q_{i|j(i)} = (n_{i|j(i)} - a_{i|j(i)} + 0.5) / (N - A + 1)$

         $b = ((p_{j(i)}-p_{i|j(i)})/(p_{j(i)}*(1-p_i))) - ((q_{j(i)}-q_{i|j(i)})/(q_{j(i)}*(1-q_i)))$

         $c = ((p_{i|j(i)}*(1-q_{i|j(i)}))/(q_{i|j(i)}*(1-p_{i|j(i)}))) - ((p_i*(1-q_i))/(q_i*(1-p_i))) - ((p_{j(i)}*(1-q_{j(i)}))/(q_{j(i)}*(1-p_{j(i)})))$

         RSV = RSV + b + c
     - 4.4.3. Rank structures in decreasing order of their RSV
5. Retrieve top 100 compounds from the ranked list and obtain the following
   - 5.1. V = Total number of active structures in the top 100
   - 5.2. Determine V_i
     - 5.2.1. For each screen i
       - 5.2.1.1. V_i = Total number of structures which is a subset of V containing bit b_i
     - 5.2.2. For each pair in expanded query
       - 5.2.2.1. $V_{i|j(i)}$ = Total of structures which is a subset of V containing both bit b_i and $b_{j(i)}$
   - 5.3. Load dependence tree for the next set and expand query.
   - 5.4. Calculate similarity for every structure in that set
     - 5.4.1. RSV = 0.0
     - 5.4.2. For every common bit shared by both query and structure
       - 5.4.2.1. $p_i = (V_i + 0.5) / (V + 1)$
       - 5.4.2.2. $q_i = (n_i - V_i + 0.5) / (N - V + 1)$
       - 5.4.2.3. RSV = RSV + $(p_i*(1-q_i))/(q_i*(1-p_i))$
       - 5.4.2.4. Find parent of matched bit in dependence tree. If found and appear in structure bit string then

         $p_{j(i)} = (V_{j(i)} + 0.5) / (V + 1)$, $q_{j(i)} = (n_{j(i)} - V_{j(i)} + 0.5) / (N - V + 1)$

         $p_{i|j(i)} = (V_{i|j(i)} + 0.5) / (V + 1)$, $q_{i|j(i)} = (n_{i|j(i)} - V_{i|j(i)} + 0.5) / (N - V + 1)$

         $b = ((p_{j(i)}-p_{i|j(i)})/(p_{j(i)}*(1-p_i))) - ((q_{j(i)}-q_{i|j(i)})/(q_{j(i)}*(1-q_i)))$

         $c = ((p_{i|j(i)}*(1-q_{i|j(i)}))/(q_{i|j(i)}*(1-p_{i|j(i)}))) - ((p_i*(1-q_i))/(q_i*(1-p_i))) - ((p_{j(i)}*(1-q_{j(i)}))/(q_{j(i)}*(1-p_{j(i)})))$

         RSV = RSV + b + c
     - 5.4.3. Rank structures in decreasing order of their RSV
6. Repeat step 5 for set 3 and 4.

Figure 3.16 BD model combinational query result algorithm

3.5.3 Performance Evaluation

Performance evaluation of each PM approach will be computed by determining the average total number of actives at top 400 of the list. It is then compared to the average total number of actives at top 400 of the VSM approach. A good similarity searching system is denoted if there are quite a number of active structures on the top 400 of the list.

3.6 Hardware and Software Requirements

In this section, hardware and software requirement of this project are stated. The following is the list of hardware and software used to carry this project:

Table 3.4: Software Requirement

Software	**Details**
1. Microsoft Visual C++ 6.0	All similarity searching programs will be developed using the C++ language. Thus Visual C++ is used because it provides a stable environment to develop a program and an extensive help file.
2. Microsoft Office XP	This software package will be used to prepare reports and presentation file.
3. Microsoft Project 2000	This software is a popular project management tool. It is used to generate Gantt charts for this projects planning.
4. Microsoft Windows XP	As the operating system.

Table 3.5: Computer Specification

Component	Specification
Processor:	Intel Pentium IV 2.8 GHz
Memory:	512MB
Hard disk:	40GB

3.7 Discussion

This chapter gives details on how experiment is carried out to determine whether the proposed approach have given us better performance result compared to the existing similarity searching method. The aim of an effective retrieval system is to respond to a query so as to retrieve most active chemical structure, while retrieving very few inactive structures. A series of *simulated similarity searching* is conducted for both existing and proposed approach. This experiment design has been used on almost all research that involves determining the effectiveness of similarity searching system. However, most experiment involves manipulating between the main requirements of similarity searching which is the structural descriptor and similarity coefficient, to determine which is superior (e.g. Chen and Reynolds, 2002; Salim, 2002). Hence the same approach is also taken up in this project.

We have chosen to base our comparison to VSM-based similarity searching with 2D screens as its structural descriptor and *Tanimoto* coefficient as its similarity measure. 2D screens particularly dictionary-based bit string are used here. In Chapter 2, we have already discussed why this representation scheme is preferred rather than the other alternative of 2D screen which is the very dense hashed fingerprint.

For similarity measure, the *Tanimoto* coefficient is used. It is an association coefficient where it is consider a common presence of attributes as evidence of similarity. Association coefficient is also generally preferred to than the distance coefficients. The difference between association and distance coefficient is that the latter effectively consider a common absence of attributes as evidence of similarity, whereas the former do not. Chen and Reynolds (2002) conducted experiments and concluded that common presence of certain structural features is the primary factor in determining similarity between two chemical structures. However, absence of features may also be important in some cases but is at best considered secondary.

The proposed approaches for this work involve the PM (i.e. BIR and BD model). It has already been discussed in detail in Chapter 2. However, now we are no longer dealing with documents but chemical structures. Applying PM in chemical database environment is very straight forward, particularly due to its similarity in representing object. The following diagram summarises the framework in applying PM in chemical databases:

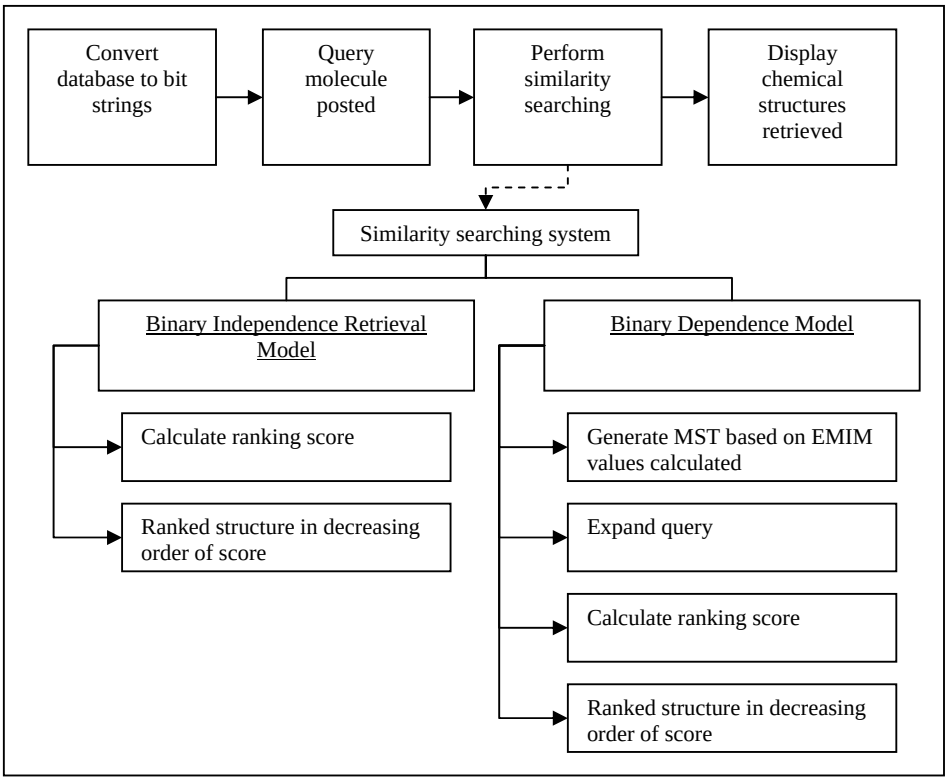


Figure 3.17 Proposed framework

3.8 Summary

In the effort to improve chemical retrieval system, PM was proposed. Both independent and dependent assumption of bits were considered, that is by applying BIR and BD Model in chemical database environment. In this chapter, processing steps have been discussed for each model. Overall, this project involves converting database to bit strings, performing similarity searching when user posts a query and displaying the result. Lastly, the performance of each approach is evaluated. Results and analysis of the performance evaluation is presented and discussed in Chapter 4.

CHAPTER 4

RESULTS AND DISCUSSIONS

In Chapter 3, steps taken in conducting experiment in this project were discussed. Thus, Chapter 4 presents the results of these experiments. This chapter is very important as the outcomes will prove whether the proposed approaches are more favourable in chemical database processing. The outline of this chapter is as follows: As mentioned in previous chapters, the proposed PM-based similarity searching system will be compared with the existing method. Hence, there are three groups of result belonging to the VSM, BIR and BD model. There are 1049 active compounds (i.e. both CM and CA) posted as target compound. The output of each similarity searching system is a series of ranked list of structures, and stored in the following output files: *VSMResult.txt*, *BIRResult.txt* and *BDResult.txt*. Format of output file is as depicted in Figure 4.1. From each ranked list, we acquire the performance evaluation for each method (Figure 4.2). Next, the average of 1049 (target compounds posted) performance evaluation is calculated, which consist of the GH score, initial enhancement and total active structures at top 5% of the ranked list, which is from the first experiment. The result of the second experiment is also shown here which includes the average total active structures at top 400 of the ranked list. Discussion in this chapter emphasizes on the critical analysis of the results. This is done by comparing the results of all three approaches and stating some observation based on it.

{Active molecule as target molecule}
Query posted: 10100101000000000010000000000000000000000000000000000…

{Structure ID}	***{Compound name}***	***{Similarity / Ranking Score}***
1	aids99_CA_STR1	1.0000
339	aids99_CM_STR193	0.9664
156	aids99_CA_STR282	0.8760
3	aids99_CA_STR102	0.8618
23	aids99_CA_STR125	0.8346
707	aids99_CM_STR58	0.8293
499	aids99_CM_STR36	0.8160
4097	aids99_CI_STR3895	0.7984
232	aids99_CA_STR8	0.7692
382	aids99_CM_STR238	0.7541
:	:	:

Figure 4.1 File format of output file.

{Query No.}
Query no. 1
{GH Score section consisting of values for recall, precision, GH score, false positive, false negative}
GH Score:

Recall	Precisions	GHScore	False+	False-	
12.3928	44.9827	28.6877	159	919	***{Values at 5% of structure retrieved}***
16.3012	29.5848	22.9430	407	878	***{Values at 10% of structure retrieved}***
20.4004	24.7113	22.5558	652	835	***{Values at 15% of structure retrieved}***
25.5481	23.2035	24.3758	887	781	***{Values at 20% of structure retrieved}***
30.1239	21.8837	26.0038	1128	733	***{Values at 25% of structure retrieved}***
34.7950	21.0739	27.9345	1367	684	***{Values at 30% of structure retrieved}***

Initial enhancement: 2633 ***{No of structures retrieved before half of the active structures are found.}***
No of actives at top 5%: 130 ***{No of active structures retrieved at top 5% of the ranked list.}***

Query no. 2
GH Score:

Recall	Precisions	GHScore	False+	False-
5.4337	19.7232	12.5785	232	992
10.9628	19.8962	15.4295	463	934
15.2526	18.4757	16.8642	706	889
19.7331	17.9221	18.8276	948	842
26.2154	19.0443	22.6299	1169	774
30.9819	18.7644	24.8732	1407	724

Initial enhancement: 2926
No of actives at top 5%: 57
…

Query no. 1049
GH Score:

Recall	Precisions	GHScore	False+	False-
7.6263	27.6817	17.6540	209	969
13.4414	24.3945	18.9179	437	908
19.1611	23.2102	21.1856	665	848
26.8827	24.4156	25.6492	873	767
32.9838	23.9612	28.4725	1098	703
39.0848	23.6721	31.3784	1322	639

Initial enhancement: 2399
No of actives at top 5%: 79

Figure 4.2 Sample evaluation result for similarity searching system.

4.1 Results of VSM-based Similarity Searching

Table 4.1 shows the average result of VSM-based similarity searching in terms of four evaluation merits discussed earlier. In the first experiment, readings of GH scores are taken on each 5% interval of structure retrieved, which are 5%, 10%, 15% …30%. Readings stop at 30% of the structures retrieved. This means that the final GH score value is obtained when 1732 compounds are retrieved. More than this value is not considered because normally user will only look at most the top 1000 compounds. As seen in the table below, the GH score increases on each level. This is expected as when we retrieved more structure we obtain more actives. While computing GH scores, we can also acquire the values for false negative and false positive on each level. This is to find out the number of active and inactive in the ranked list, respectively. For initial enhancement we consider the number of chemical structure retrieved before half of the actives are found. The VSM-based similarity searching attains an average of 2705 compounds for this evaluation criterion. Next, we can see that this approach returns an average of 73 active compounds on top 5% of its ranked list. For the second experiment, the VSM-based similarity searching obtains an average of 95 active structures at top 400 of its list.

Table 4.1: Summary of VSM Result

Experiment 1:

	5%	10%	15%	20%	25%	30%
Average GH Score	16.26	17.11	18.95	21.22	23.59	26.02
Average False +	215	450	686	921	1157	1391
Average False -	975	921	869	815	762	708

Average initial enhancement **:** 2705

Average number of actives at top 5% **:** 73

Experiment 2:

Average number of actives at top 400 **:** 95

4.2 Results of BIR-based Similarity Searching

Analogous to the results in the previous section, Table 4.2 shows the average result of BIR-based similarity searching in terms of the three evaluation merits. As seen in the table below, the GH score from the first experiment also increases on each level. For the number of chemical structure retrieved before half of the actives are found, the BIR-based similarity searching attains an average of 1917 compounds for this evaluation criterion. This approach also returns an average of 133 active compounds on top 5% of its ranked list. Finally, for the second experiment, the BIR model retrieves an average of 155 actives at top 400 of its list.

Table 4.2: Summary of BIR Model Result

Experiment 1:

	5%	10%	15%	20%	25%	30%
Average GH Score	29.43	29.51	31.06	32.97	35.14	37.27
Average False +	155	358	571	792	1016	1244
Average False -	915	829	754	686	621	561

Average initial enhancement **:** 1917

Average number of actives at top 5% **:** 133

Experiment 2:

Average number of actives at top 400 **:** 155

4.3 Results of BD-based Similarity Searching

The summary of the average result of BD-based similarity searching is shown in Table 4.3. GH scores increase on each level for this approach and obtains an average of 1859 compounds for initial enhancement. Next, we can see that this

approach returns an average of 141 active compounds on top 5% of its ranked list. For the second experiment, the BD model obtains an average of 160 actives at top 400 of its list.

Table 4.3: Summary of BD Model Result

Experiment 1:

	5%	10%	15%	20%	25%	30%
Average GH Score	31.20	30.86	32.26	34.19	36.18	38.16
Average False +	147	348	559	779	1004	1233
Average False -	907	819	742	673	609	550

Average initial enhancement **:** 1859

Average number of actives at top 5% **:** 141

Experiment 2:

Average number of actives at top 400 **:** 160

4.4 Discussion

In this section, two issues need to be determined. The first being whether the PM-based similarity searching overcomes the existing approach. If so, which of the probability models proposed is more superior in the chemical database environment. Hence, in each performance criterion, these two issues are taken into consideration. The following is the comparison made for all three approaches of similarity searching involved in this work, with respect to the performance criterion below:

a) Experiment 1: Comparing the Effectiveness of Similarity Searching Methods

- GH Score

In the following figure, GH score values at each 5% level of the structure retrieved are plotted for all the similarity searching method. As seen in the graph, we can conclude that both PM approaches outperform the existing system.

As GH score gives quantitative measure of the ranked list quality, we can confirm the PM approaches is substantially more selective than the others without compromising present of actives too much. The graph also shows that the BD model's GH score performance exceed the BIR model but only slightly.

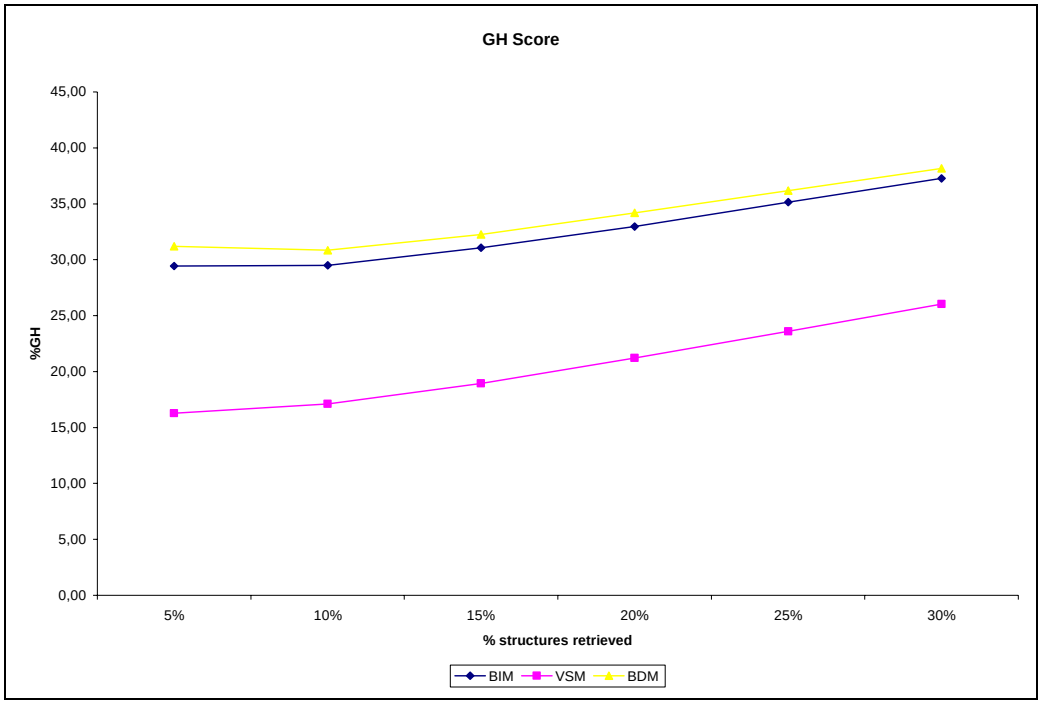


Figure 4.3 GH score analysis for VSM, BIR and BD model.

- False Positive and False Negative

Figure 4.4 shows the number of inactive structures in the ranked list, whereas Figure 4.5 shows the number of actives not in the ranked list.

This is referred to as the false positive and false negative of the ranked list. In both cases, the VSM has the most false positive and false negative in its list. The performance of both BIR and BD model on the other hand is much better. However, BD model has the least number of false positive and false negative in its ranked list, with a decrease of 8 to 13 structures compared to the BIR model.

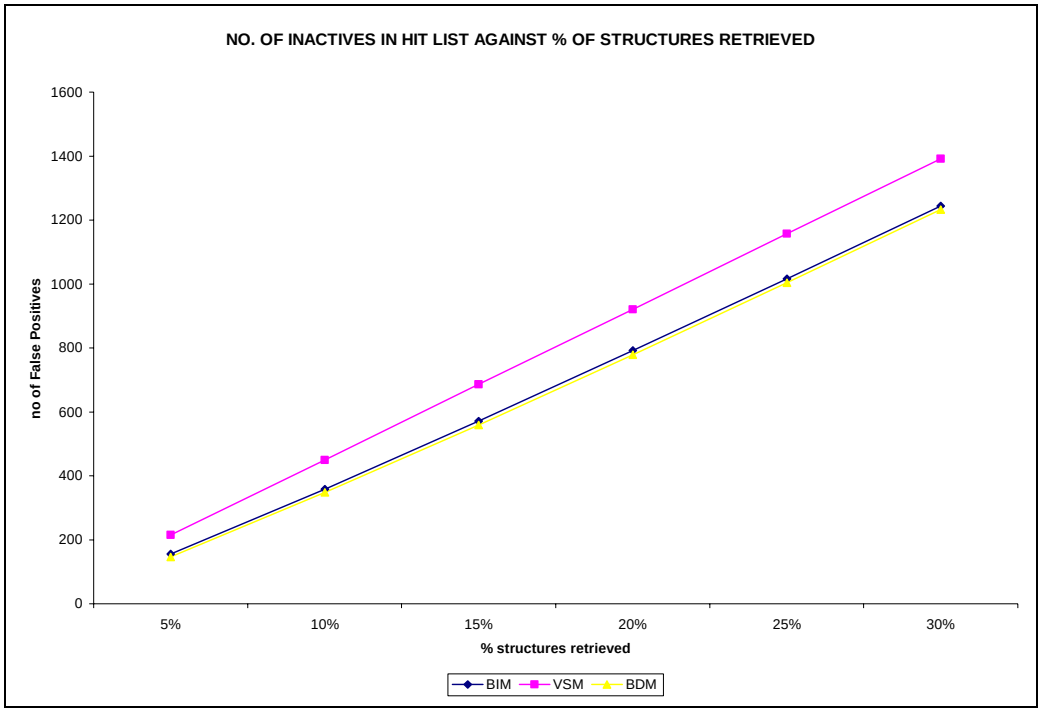


Figure 4.4 False positive analysis for VSM, BIR and BD model.

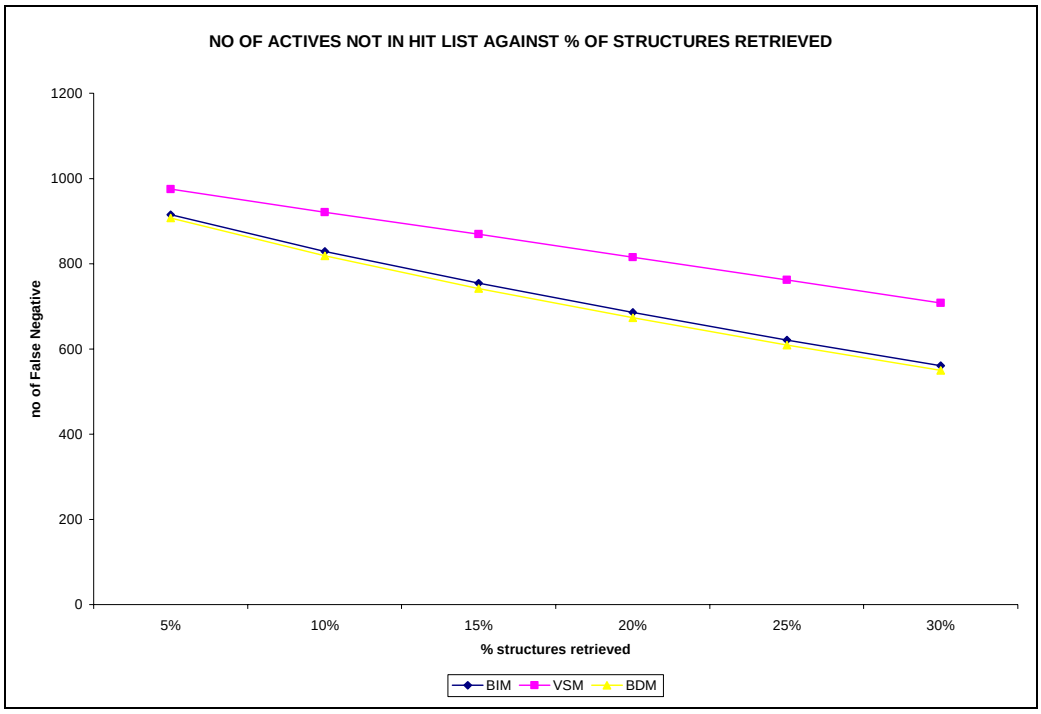


Figure 4.5 False negative analysis for VSM, BIR and BD model.

- Average Initial Enhancement

  As discussed in Chapter 3, initial enhancement refers to the number of chemical structure retrieved before half of the actives are found. Hence, the performances of similarity searching methods are comparable, with the superior system having less value of initial enhancement. The figure below shows us that again the VSM has the highest value of initial enhancement. It retrieves approximately 800 more structures compared to the PM approaches.

  Here again we can see that BD model is more superior in term of average initial enhancement. BIR model retrieves 58 more structures before half of the actives are found compared to the BD model.

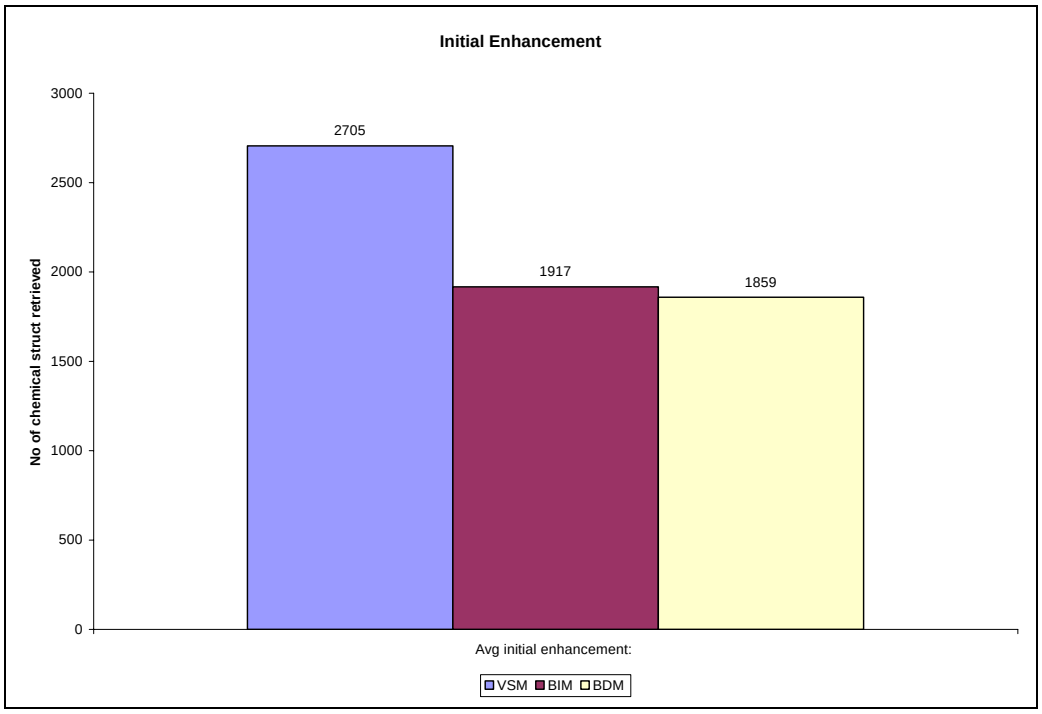


Figure 4.6 Initial enhancement analysis for VSM, BIR and BD model.

- Average Total of Actives at 5% of List.

A good similarity searching system is also denoted by the number of active structures at the top 5% of its list. Top structures of the list normally show the nearest neighbours of the target molecule. More actives on this part of ranked list can help elevate the lead optimisation process, where initial lead compound are sought in order to find better compounds. The following shows us that the PM approaches have given more actives than the VSM. It also suggests that the BD model is a more effective similarity searching system with slight improvement (8 active structure more) than the BIR model.

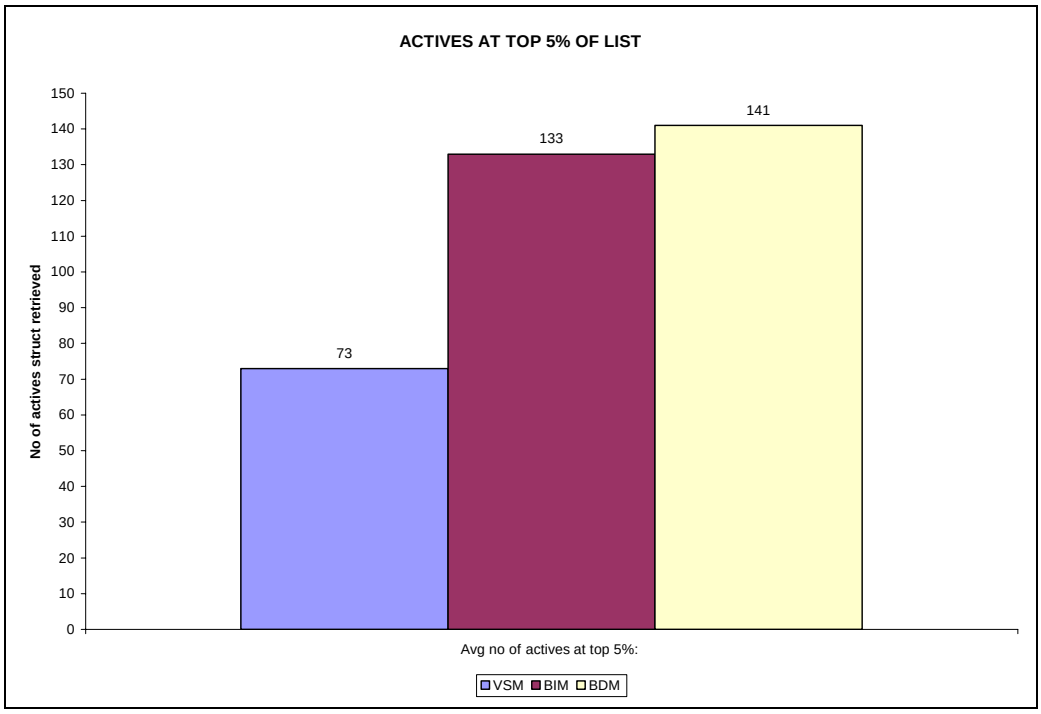


Figure 4.7 Average number of actives in top 5% for VSM, BIR and BD model.

b) Experiment 2: Comparing the Performance of Query Fusion Result of Similarity Searching Methods

- Average Total of Actives at Top 400 of List.

The purpose of query fusion is to improve the performance of similarity searching based on combining chemical target in an iterative similarity searching to estimating probability instead of obtaining from the entire collection. It is then compared to the average total number of actives at top 400 of the VSM approach. A good similarity searching system is denoted by the number of active structures at the top 400 of its list. The following shows us that the PM approaches have given more actives than the VSM. It also suggests that the BD model is a more effective similarity searching system with five active structures more than the BIR model.

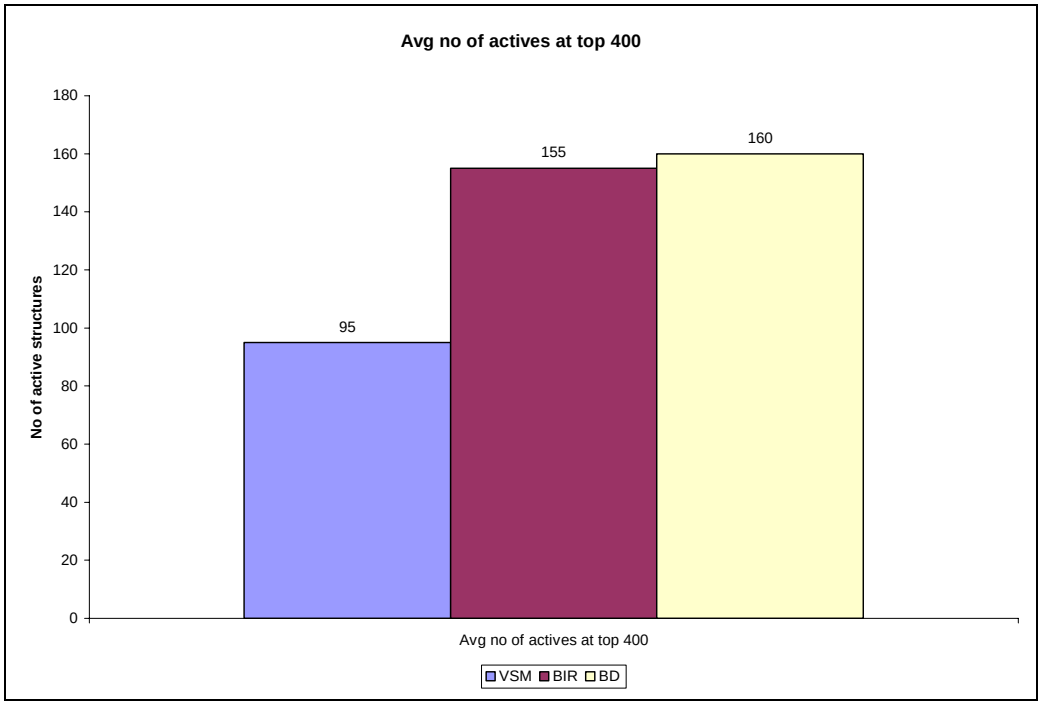


Figure 4.8 Average number of actives in top 400 for VSM, BIR and BD model.

4.5 Summary

The proposed approaches for similarity searching are implemented according to the steps listed in the methodology. Based on its ranked list, evaluation is done to determine which method is better. Four main evaluation merits were considered here which are the GH score, initial enhancement, total actives at top 5% and total actives at top 400. They are needed as to resolve the following issues: 1) Does PM-based similarity searching really overcomes the existing similarity searching; and 2) Which of the probability model proposed, perform better in the chemical database environment. Results in this chapter have shown that in all four evaluation merits, the PM is superior, with significant improvement over the VSM. Other than that, we can also conclude that the theoretical stronger BD model has a slight improvement over the BIR model, which has a weaker notion of dependence.

CHAPTER 5

CONCLUSION

5.1 Summary of Work

IR has taken the centre stage when the Internet was introduced. Now, with endless repository of knowledge and culture, searching for information can be tedious. Standard *Boolean* logic approaches are no longer sufficient for retrieving information. Hence, many new retrieval models were introduced. VSM is currently the most popular model used in major information services and the WWW. Current similarity searching of chemical compounds also applies similar approach as the vector space. Since there are similarities in the way that chemical and textual database records are characterised, it is no wonder why algorithms developed for the processing of textual databases can also be applied in chemical structure database processing database.

In the effort of improving the chemical retrieval system, PM is proposed for this project. It has strong theoretical basis and in principle should give the best performance of relevance. Since there are no known application of probability model in similarity searching, hence this statement is yet to be proven.

Among the PM approaches proposed is the BIR and BD model. BIR model was chosen, as it is the simplest probability model there is. It was initially considered to see whether PM could be indeed applied in the chemical database environment. The success of the implementation of BIR model has encourage the PM to be seriously considered for similarity searching.

PM was proposed to overcome the VSM limitations, particularly its bit independence assumption. As the BIR model offers linked-dependence, which is a weaker assumption of bit dependence, hence it is obvious to extend this work by repeating experiments with a dependence model i.e. BD model.

Results from experiments carried out have determined that PM really did perform better than the existing similarity searching. It gave better result in all the evaluation criteria thus confirming this statement. In terms of which probability model performs better, the BD model shown some improvement over the BIR model. Thus, the findings of this work have help close the knowledge gap with hope that it can help contribute to the improvement of the current similarity searching system.

5.2 Future Work

The works of this project can be further enhanced in many ways. Additional experiments can also be carried out to validate further the findings of this project. Since, various other techniques could be explored to find better alternatives to current similarity searching; hence, works need to be done before a practical implementation can be built upon the findings.

Take for example, there many other probability models that appeal for future consideration. The non-binary independence model (Yu and Lee, 1986; Yu, Meng and Park, 1989) for instance, captures the information about the number of occurrences of a term within a document as well as the number of document having the term. It has yield significant improvement over BIR model and is one of the ways to alleviate the consequences of the term independence assumption. Hence, this model should also be considered for future research. Other models such as inference network or belief network can also be studied.

Experiments in this project could also be carried out on other chemical database available. Chen and Reynolds (2002) mentioned that the NCI AIDS database is not a perfect data set for evaluation but it is the best data set available. Hence, to complement the findings, other chemical database should also be considered. For example the MDDR (MDL Drug Data Report) database. It is a licensable database and contains diverse drug-like molecules to which most have been assigned a therapeutic category (Molecular Design Ltd.). As the NCI AIDS database gives thorough sampling of a particular region in chemical space, MDDR in turn gives a broad coverage of chemical space that is pharmaceutically relevant.

In addition, other bit string representation can also be used in this project to represent chemical compounds, for example the Daylight fingerprint (James, *el. al*, 2000) and the UNITY 2D bit strings (Tripos Inc., 1999). The Daylight fingerprint is a 2048-bit hashed fingerprint that encodes each atom's type, augmented atoms and paths of length 2 to 7 atoms. One of the advantages of hashed fingerprint is that it is not library biased. However, it does experience some loss of information. Meanwhile, UNITY 2D bit-string, unlike Daylight fingerprint that hashes all recorded information over the whole length of the fingerprint, keeps information from different-length paths distinct. Different parts of the bit string, record information of fragments of length 2 to 6. A few generic structural keys are added for some common atoms and bond types, producing a bit string of 992 bits.

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